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TO CLINICAL RADIOLOGY AND
ALLIED SCIENCES

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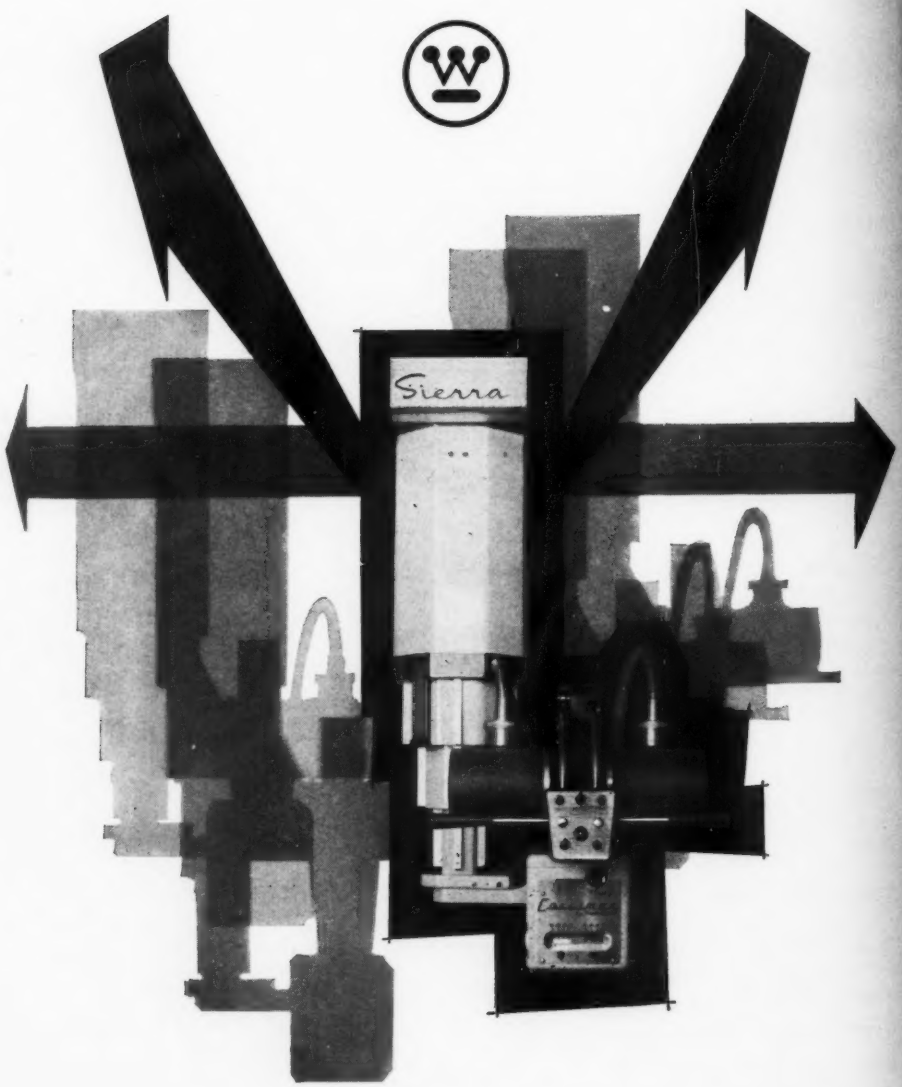

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Hemobilia[1]

CAPT. STEFAN C. SCHATZKI, MC, USA[2]

HEMOBILIA, which may be defined as hemorrhage into the biliary tract (14), is an uncommon cause of gastrointestinal blood loss. Numerous reports have described the chronic loss of blood that occurs with neoplasms of the ampulla of Vater, biliary stones, and other lesions of the biliary tract, but *massive* hemobilia, with severe acute gastrointestinal hemorrhage as the presenting symptom, is rare.

Several articles have been published on the various causes for massive biliary hemorrhage, chiefly in surgical journals; no discussion of this problem has appeared in the radiological literature. Since most patients with severe gastrointestinal hemorrhage are examined in the department of radiology by means of various contrast studies, it is felt that an awareness of this unusual source of bleeding should be of interest and value. This report will review the various causes of massive hemobilia and discuss in more detail traumatic hemobilia as illustrated by a case.

REVIEW OF THE LITERATURE

The most common causes for massive hemobilia are aneurysm of the hepatic artery and liver trauma. To date there have been reported approximately 50 cases of aneurysm and 20 of trauma associated with severe gastrointestinal hemorrhage.

Sixty per cent of aneurysms of the hepatic artery have been thought to be secondary to infection; arteriosclerosis and trauma are less common causes. The preoperative diagnosis of the aneurysm is usually impossible. Grant *et al.* (4), in their study of hepatic artery aneurysms, found pain, often mimicking biliary colic, in 80 per cent, hemobilia in 63 per cent, and jaundice in 55 per cent. Other nonspecific symptoms, including indigestion and flatulence, also occur. In a rare case, the liver may be enlarged, with a pulsating tumor, a palpable thrill, and a systolic bruit. These last signs, which should suggest the diagnosis, are most uncommon. If the aneurysm lies extrahepatically, the diagnosis is obvious at surgery. With an intrahepatic aneurysm, however, the necessity of an operative arteriogram arises. The gastrointestinal hemorrhage in these cases is due to erosion of the aneurysm into either the biliary tract or both the biliary and the gastrointestinal tract. Mackay and Page (9) have discussed the treatment of this condition thoroughly.

Causes of massive hemobilia other than aneurysm or trauma are rare. Fisher and Creed (3) described a primary hepatoma which led to severe gastrointestinal bleeding and to biliary obstruction by an intrabiliary blood clot. Similarly, gallbladder

[1] Accepted for publication in March 1961. This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any endorsement of the opinions advanced or any recommendation of such products as may be named.

[2] Assistant Chief, Diagnostic Section, Radiology Service, Walter Reed General Hospital, WRAMC, Washington 12, D. C.

tumors (5) and bile duct adenoma (19) have been reported as causes of massive gastrointestinal hemorrhage. At least 3 cases have been secondary to the placing of a T-tube in the common bile duct (10, 13). In the case reported by Manfredi (10) a T-tube introduced into the common duct following a cholecystectomy led to erosion into the hepatic artery and exsanguination.

Although minimal bleeding may occur rather frequently from biliary stones, massive gastrointestinal hemorrhage arising from inflammatory disease of the gallbladder or from gallstones is unusual. It has been described in acute hemorrhagic cholecystitis (18), infarction of the wall of the gallbladder (2), ulceration of the gallbladder wall or biliary tree by gallstones (7), and a form of polypoid growth of the gallbladder, termed "cholecystitis glandularis proliferans" (6). One case has been reported in which a gunshot wound led to a fistula between the common bile duct, the portal vein, and the hepatic artery (11).

Numerous other conditions have been listed as causes of biliary hemorrhage (8). Among these are acute yellow atrophy of the liver, hemangioma of the liver, cavernous transformation of the portal vein, and portal vein varices. No evidence could be found, however, incriminating any of these as a source of *massive* gastrointestinal bleeding.

TRAUMATIC HEMOBILIA

Sparkman (15, 16), was able to collect 14 cases of traumatic hemobilia. Since his classical articles appeared in 1953 and 1954, 3 more cases have been found in the English literature (1, 12, 17) and several in foreign publications, thus bringing the total to about 20 cases. Traumatic hemobilia follows nonpenetrating injury to the abdominal wall. In some of these cases the trauma was not severe and did not lead to any emergency action at the time of injury. Approximately 50 per cent of the cases, however, required emergency surgery for laceration of the liver.

Sparkman called attention to a triad consisting of abdominal injury, gastrointestinal hemorrhage, and biliary colic which should lead to a high suspicion of traumatic hemobilia. While the initial episode of hemorrhage may occur within a few days of the injury, more characteristically it is delayed for several weeks, a lapse of time which has usually prevented the clinician from associating the two events. The hemorrhage is heralded by severe abdominal pain, often biliary in nature. To the patient, this pain is characteristic, and he is able to warn his physician when the next hemorrhage will occur. One three-and-a-half-year-old girl (15) successfully alerted her doctors immediately before episodes of bleeding that sent her into shock. Clinical evidence of blood loss follows soon after the onset of the pain. As melena, hematemesis, and possibly shock occur, the pain tends to abate. It is thus felt to be related to the passage of blood through the biliary tract.

In this syndrome, episodes of blood loss occur with a distinct periodicity even though the intervals between attacks tend to vary. Jaundice is a common temporary finding and is thought to be the result of biliary obstruction by blood clots. This symptom-complex of periodic severe abdominal pain, followed by gastrointestinal hemorrhage which tends to relieve the pain, and jaundice has occurred with such frequency in the reported cases that its presence in a patient with any history of trauma should suggest the diagnosis.

An intrahepatic cavity that periodically empties its contents into the biliary tract is responsible for this syndrome. The original trauma undoubtedly results in some necrosis of liver parenchyma. Sparkman felt that as necrosis occurs, the devitalized liver tissue leads to further breakdown of liver parenchyma; the vascular oozing continues, and some secondary infection may ensue. These all combine to produce an intrahepatic cavity, the contents of which are under considerable pressure. Periodically, the pressure in the cavity becomes sufficient to allow decompression into the biliary tree and the clinical syndrome of pain and hemorrhage results.

While most of the cases have been due to such an intrahepatic cavity, some examples of pseudocavities produced by oversewing of an hepatic laceration have also been reported. In these cases, the repair of the laceration has resulted in a cavity on the surface of the liver, the mechanisms otherwise being presumably the same as in the intrahepatic cavities.

The operative approach to this entity has been discussed by Sparkman (15) and will be reviewed in a surgical report from Walter Reed General Hospital. In the 14 cases that Sparkman collected, the mortality rate was over 50 per cent. In the last 5 cases reported in the English literature, there were 4 survivals. This indicates the importance of early diagnosis and surgical measures. Various operative procedures have been used. These include gauze packing of the hepatic cavity, ligation of the right hepatic artery, cholecystectomy, and, in our case, resection of the involved portion of the liver.

CASE REPORT

A 4 1/2-year-old girl was in good health until June 7, 1960, when she was thrown against the dashboard of an automobile in which she was riding. She suffered a minor scalp laceration and also complained of some mild abdominal pain. On June 21 the pain became severe and was followed by vomiting. Examination on admission to the hospital disclosed hepatomegaly and mild jaundice; the bilirubin had risen to 7 mg. per 100 ml. On June 24 and again on June 29 massive gastrointestinal hemorrhages occurred, which required transfusion. A gastrointestinal series showed no abnormalities except that the stomach was displaced posteriorly, presumably by the liver (Fig. 1). The jaundice by this time had cleared.

Because of recurrent hemorrhages, the patient was transferred on July 1 to another hospital. On July 3, she had another bout of hematemesis and melena, and a unit of blood was required. To determine the source of bleeding an exploratory laparotomy was performed. The left lobe of the liver proved to be enlarged, and a "lump" was palpable on its posterior surface. There was no blood in the peritoneal cavity. Because it was felt that the bleeding arose from the left lobe of the liver, due to a subcapsular hematoma, the left hepatic artery was ligated.

The patient did well until July 9, when she had the next of multiple recurrent episodes of hematemesis and melena. The hemorrhages occurred on July 9, 19, and 25, and on Aug. 4, 15, and 28. On each of these occasions the symptoms were the same: severe cramping abdominal pain followed almost immediately by melena and/or hematemesis and a shock-like condition, with rising pulse, lowered blood pressure, and a drop in hemoglobin. During these episodes the patient received 12 units of blood. In the intervals she was asymptomatic.

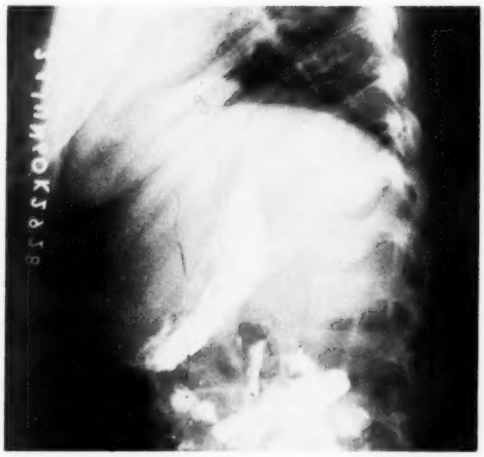

Fig. 1. Upper gastrointestinal examination on June 24, 1960: lateral view. The body of the stomach appears slightly displaced posteriorly, presumably by an enlarged liver.

Multiple liver function studies were made during the months of July and August and in all the findings were within normal limits. There was no recurrence of the jaundice present at the time of the original hospitalization, but because of the repeated gastrointestinal hemorrhages, the patient was transferred to Walter Reed General Hospital. There, except for a liver that was palpable two fingerbreadths below the right costal margin, her physical examination was within normal limits. Hematologic studies were also normal. Liver function studies were reported as showing: bilirubin, 1.0 mg. per 100 ml.; cephalin flocculation, negative; thymol turbidity, 2+; alkaline phosphatase, 32.2 units. A repeat gastrointestinal series again showed no abnormalities except for some posterior displacement of the stomach. On Sept. 9 another exploratory laparotomy was performed, and a firm, indurated mass, measuring 5 cm., in an enlarged left lobe of the liver was noted. Blood was found in the biliary tree, and a necrotic piece of liver tissue floated in the left hepatic duct, thus confirming a communication between the hematoma cavity and the biliary system. An operative cholangiogram showed the right lobe of the liver to be normal, while the left lobe contained a large irregular cavity in direct communication with the left hepatic duct (Fig. 2). A left hepatic lobectomy was performed, and the presence of a cavity containing necrotic

Fig. 2. Operative cholangiogram. The right hepatic duct appears normal. The contrast medium enters a large irregular cavity from the left hepatic duct.

liver tissue was confirmed. The medial-most portion of the hematoma cavity which remained after resection was not sutured tightly, and two Penrose drains were left in place. Postoperatively, the patient did well, and the drains were removed in two weeks. The pathological specimen confirmed the operative impression. A large cavity which had a fibrous wall and contained blood and a small amount of necrotic liver was found in the left lobe of the liver (Fig. 3). The child recovered satisfactorily and four months later was reported well.

DISCUSSION

The biliary tract is an uncommon yet important source of massive gastrointestinal hemorrhage. In many cases, the diagnosis cannot be made preoperatively, but in certain instances, it can be suspected from the clinical findings. The triad of trauma, abdominal pain consistent with biliary colic, and gastrointestinal bleeding should lead to the consideration of traumatic hemobilia. The patient may be able to tell the physician when an episode of bleeding will occur because of the premonitory pain similar to that experienced prior to a previous hemorrhage. Gastrointestinal blood loss, for which no other source has been found, in association with somewhat atypical pain, consistent with a biliary source, should suggest the possibility of one of the other previously enumerated sources of biliary hemorrhage.

Gastrointestinal bleeding from these uncommon causes may prove fatal if not recognized and treated properly. In most cases, there is probably no certain way of diagnosing the condition before surgery. Scintillation scanning of the liver might detect the hepatic cavity which is the source of posttraumatic hemobilia. Retrograde catheterization of the aorta (Seldinger technic) and opacification of the hepatic artery might be helpful in cases of gastrointestinal bleeding of unknown etiology where there is clinical suspicion of an hepatic-artery aneurysm. If no other cause for a gastrointestinal hemorrhage is found on exploration, the surgeon should investigate the biliary tract as a possible source. Should this contain blood, an operative hepatic-artery arteriogram should be obtained, and, if necessary, operative cholangiography should follow. In many of the cases reported, especially in those with traumatic hemobilia, several exploratory procedures have been performed in an attempt to find the cause of gastrointestinal hemorrhage, and the failure to find the source at surgery has, on several occasions, led to death.

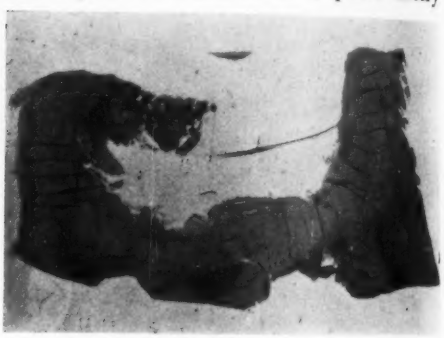

Fig. 3. Photomicrograph of the specimen, demonstrating the hepatic cavity with surrounding liver necrosis.

The knowledge that the biliary tract may serve as a source of severe and fatal gastrointestinal blood loss may allow the radiologist to direct the surgeon to undertake the investigations necessary for diagnosis and treatment of these uncommon causes of gastrointestinal hemorrhage.

CONCLUSIONS AND SUMMARY

1. Hemobilia, or hemorrhage into the biliary tract, may result in massive gastrointestinal bleeding. Aneurysm of the

hepatic artery and post-traumatic liver cavities are the most common sources, though other biliary lesions have occasionally been found responsible. The knowledge that hemobilia exists will help prevent the negative abdominal exploration and possible subsequent exsanguination that have occurred frequently in the past in patients with severe gastrointestinal hemorrhage originating in the biliary tract.

2. Traumatic hemobilia is associated with severe abdominal pain, massive periodic gastrointestinal blood loss, and a history of abdominal trauma. The details of this syndrome have been presented in a report of a single case in a girl four and a half years old.

3. The radiologic procedures that may be utilized to diagnose these lesions in the preoperative and operative periods have been briefly enumerated.

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REFERENCES

1. BROKER, H. M., AND HAY, L. J.: Hemobilia Following Blunt Trauma to Liver. Minnesota Med. **38**: 333–334; 336, May 1955.

2. ESAU: Hämorrhagischer Wandinfarkt der chronischen Steingallenblase mit Blutungen in den Darm. Cited by Lichtman (8).

3. FISHER, E. R., AND CREED, D. L.: Clot Formation in Common Duct: An Unusual Manifestation of Primary Hepatic Carcinoma. Arch. Surg. **73**: 261–265, August 1956.

4. GRANT, J. L., FITTS, W. T., JR., AND RAVDIN, I. S.: Aneurysm of the Hepatic Artery. Report of Two Cases and Consideration of Surgical Treatment. Surg., Gynec. & Obst. **91**: 527-532, November 1950.

5. HUDSON, P. B., AND JOHNSON, P. P.: Hemorrhage from Gall Bladder. New England J. Med. **234**: 438–441, March 28, 1946.

6. HUTCHINS, L. R., MANZER, T. T., AND STRANAHAN, A.: Massive Gastrointestinal Hemorrhage from Primary Gallbladder Disease. Northwest Med. **45**: 334–336, May 1946.

7. JUNGHANNS, H.: Blutendes ulcus in det gallenblase. Cited by Lichtman (8).

8. LICHTMAN, S. S.: Gastro-Intestinal Bleeding in Disease of Liver and Biliary Tract. Am. J. Digest. Dis. **3**: 439–445, August 1936.

9. MACKAY, A. G., AND PAGE, H. G.: Hematemesis Associated with Hemobilia. Report of a Case Due to an Intrahepatic-Artery Aneurysm, with Survival. New England J. Med. **260**: 468–471, March 5, 1959.

10. MANFREDI, D. H.: Gastrointestinal Hemorrhage Originating in the Biliary Tract. New York State J. Med. **58**: 2397–2398, July 15, 1958.

11. MARKGRAF, W. H.: Traumatic Hemobilia Associated with a Hepatoportal Biliary Fistula. A Case Report. Arch. Surg. **81**: 860–863, December 1960.

12. MORETZ, W.: Hemobilia. Exhibit Am. Coll. Surgeons, San Francisco, November 1960.

13. RABINOVITCH, J., AND RABINOVITCH, P.: Massive Bleeding from Common Bile Duct Caused by Indwelling T-Tube. Arch. Surg. **69**: 849–852, December 1954.

14. SANDBLOM, P.: Hemorrhage into Biliary Tract Following Trauma; "Traumatic Hemobilia." Surgery **24**: 571–586, September 1948.

15. SPARKMAN, R. S.: Massive Hemobilia Following Traumatic Rupture of Liver: Report of Case and Review of Literature. Ann. Surg. **138**: 899–910, December 1953.

16. SPARKMAN, R. S., AND FOGELMAN, M. J.: Wounds of Liver; Review of 100 Cases. Ann. Surg. **139**: 690–719, May 1954.

17. SPECTOR, N.: Ligation of the Right Hepatic Artery in Hemobilia. Report of a Case with Recovery. Ann. Surg. **145**: 244–248, February 1957.

18. STAHL, W. M., JR.: Gastrointestinal-Tract Hemorrhage Due to Gall-Bladder Disease. New England J. Med. **260**: 471–474, March 5, 1959.

19. TETER, L. F.: Massive Hemorrhage from Benign Adenoma of Biliary Duct Causing Death. J. Michigan M. Soc. **53**: 62–63, January 1954.

SUMMARIO IN INTERLINGUA

Hemobilia

Hemobilia, i.e. hemorrhagia ad in le vias biliari, es un causa incommun de perditas gastrointestinal de sanguine.

Le diverse causas de massive hemobilia es revistate, e hemobilia traumatic es discutite in plus grande detalio. Iste ultime es illustrate per un caso. Causas altere que aneurysmo e trauma es rar.

Hemobilia traumatic es associate con sever dolores abdominal, massive e periodic perditas de sanguine gastrointestinal, e un antecedente trauma abdominal. In le majoritate del casos il existe probabilemente nulle methodo pro diagnosticar le condition ante le intervention chirurgic. Explorar le hepate per medio de scintillation es possibilemente capace a deteger le cavitate hepatic que es le fonte del hemobilia post-traumatic. Catheterismo retrograde (technica de Seldinger) e opacification del aneurysmo de arteria hepatic es forsan de adjuta in casos in que il existe le suspicion clinic del presentia de un tal aneurysmo. Si nulle altere causa es trovate in le laparotomia, le chirurgo debe investigar le vias biliari. Si sanguine es presente in illos, un arteriogramma de arteria hepatic debe esser obtenite. Si necessari, isto debe esser sequite de cholangiographia operatori.

Lymphangiosarcoma in the Lymphedematous Arm After Mastectomy[1]

GEORGE P. KEEFER, M.D., and JACOB H. VASTINE, 2nd, M.D.

THE SWOLLEN ARM which frequently occurs after radical mastectomy for breast carcinoma has long been a difficult management problem for both the surgeon and the radiotherapist. The discomfort and the uselessness of the edematous arm may be seriously complicated by the development of a new tumor, arising long after the malignant breast neoplasm has apparently been arrested.

A highly malignant lymphangiosarcoma may develop in a chronically edematous arm. This condition was first recognized and described as a specific disease entity by Stewart and Treves in 1948, when they published details of 6 cases. Since then, 34 additional cases have been reported in the literature. It would seem likely that this tumor has occurred more often than is indicated by the number of recorded cases. Many have been seen, diagnosed, and treated but not reported. Still more have probably gone unrecognized or were possibly considered to be disseminated, recurrent, inoperable cutaneous metastases of the original breast cancer.

Lymphangiosarcoma in the lymphedematous arm has received little notice in our radiologic literature. It is the purpose of this paper not only to describe its clinical symptoms but also to emphasize the appearance of early skin changes as seen in 4 patients. If the physician is alerted to the possible existence of this malignant tumor, the diagnosis can usually be made prior to microscopic verification. Early aggressive therapy is completely dependent upon prompt recognition.

CLINICAL COURSE

The clinical details have been similar in all the cases of lymphangiosarcoma reported. With the exception of one patient, all of the women had undergone a radical mastectomy for a breast carcinoma, with or without associated postoperative roentgen therapy. Edema of the homolateral arm has usually developed shortly after mastectomy. This swelling persists and the arm becomes heavy. Motion is frequently limited, which may in itself add to the lymphatic stasis. The skin becomes thickened and brawny.

In general, the lymphedema has been present six or more years when a faint purplish-red, subdermal, macular lesion appears. At first, this seems to be a "bruise" or an area of ecchymosis with some induration, which gradually enlarges, with deep discoloration. There is a marked predilection of the lesion for the medial lower aspect of the upper edematous arm.

Similar satellite areas of discoloration develop and become confluent, forming bullous or papillomatous tumors. These frequently ulcerate and discharge a serous or serosanguineous exudate. There is usually rapid local spread of the tumors along the entire extremity and, finally, to the skin of the chest wall. Pulmonary metastases occur early.

The following 4 patients with lymphangiosarcoma of the upper extremity were seen.

CASE I: M. C., a 53-year-old white woman, underwent a right radical mastectomy at the age of forty-five for a highly anaplastic carcinoma of the breast with extensive axillary metastases. The patient received postoperative roentgen therapy to the right axilla, supraclavicular area, and anterior chest wall.

The right arm became edematous within a year after surgery, and, despite supportive measures, the edema did not regress.

Eight years after the mastectomy, a reddish, raised, erysipeloid reaction appeared on the lower medial aspect of the upper arm (Figs. 1 and 2). Within a short time, several edematous blebs were noted, which became hemorrhagic. At biopsy of the skin lesions, a diagnosis of lymphangiosarcoma was

[1] Presented at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960.

Figs. 1 and 2. Case I. Anterior and posterior views of the medial aspect of the right upper arm showing the raised, reddish, erysipeloid reaction of moderately early lymphangiosarcoma, eight years after mastectomy.

made. The patient refused radical surgery, and roentgen therapy was administered to the upper arm through 2 opposing ports. Only a small amount of treatment was given over a period of a week, for the patient believed that the disease process was accelerated by irradiation and refused to continue with it. There was no clinical or roentgen evidence of metastases in the lungs or skeletal structures.

Satellite lesions appeared within a few months over the right axilla and anterior chest wall. The condition gradually deteriorated, and death ensued, presumably from pulmonary metastases.

CASE II: M. N., aged 61, had a left radical mastectomy for carcinoma of the breast. There was no invasion of regional nodes at the time of surgery. Three months later, a nodule appeared along the line of incision. This was thought to be a recurrence of disease, and intensive roentgen therapy was given to the left anterior chest wall, left axilla, and left supraclavicular area.

Within a year moderate edema occurred in the entire left arm, gradually increasing in severity. Five years after operation, an indurated and reddened area, 2 cm. in diameter, developed in the medial aspect of the mid-third of the left upper arm (Figs. 3 and 4). The possibility of lymphangiosarcoma was suspected from the clinical appearance of the lesion, and roentgen therapy was administered. The induration subsided.

Eight months later, petechiae appeared on the skin of the left arm. These persisted and increased in number despite additional roentgen therapy. At biopsy at this time thrombophlebitis was reported. Within four months, the skin became quite leathery and turned purplish-red, and ulcerations developed (Fig. 5). The biopsy diagnosis was now lymphangiosarcoma. Despite roentgen therapy and perfusion of the arm with nitrogen mustard, the patient died

Fig. 3. Case II. Photograph five years postmastectomy, showing an indurated and reddened area on the medial aspect of the left upper arm. The appearance suggests a "bruise" and is typical of the very early lesions of lymphangiosarcoma. This lesion subsided with local irradiation.

within three months. There was no clinical or roentgen evidence of metastases. (This case will be reported in detail by Rankin, Custer and Carty.)

CASE III: S. A. underwent a right radical mastectomy for carcinoma of the breast at the age of 54. Multiple axillary nodes were involved at the time of surgery. Within a year, a nodule appeared on the right anterior chest wall. This was biopsied and proved to be a recurrence. Roentgen therapy was then administered to the right axilla, right supraclavicular area, and anterior chest.

This patient remained well for sixteen years except for edema of the arm, which developed a year after surgery. Despite supportive measures for many years, the lymphedema did not regress.

Fig. 4. Case II. Enlarged view of the "bruise" area.

Fig. 5. Case II. The arm, seven months later, after additional x-ray therapy and perfusion with nitrogen mustard.

At the age of seventy, sixteen years after mastectomy, ecchymotic areas appeared on the skin of the forearm of the edematous extremity (Fig. 6). Reddish nodules developed in these areas and gradually coalesced and ulcerated (Fig. 7). Within four months, satellite nodules were present on the right shoulder and anterior chest wall. The patient was admitted to a hospital where the consulting physician made the following diagnosis of the lesions on the right arm: "multiple metastatic nodules in the skin surrounding an area of ulceration in the right axilla and shoulder. The arm is massive and quite useless. The ulceration over the right forearm appears to be neoplastic." Because of extreme pain, the patient was submitted to a radical amputation, with removal of the entire right arm, shoulder joint, scapula, and one-half of the clavicle. On histologic examination, no evidence of carcinoma was found in any portion of the tissues removed. The final diagnosis was lymphangiosarcoma.

Despite the removal of the right upper extremity, the patient grew rapidly worse and died from metastases of the lymphangiosarcoma to the lungs.

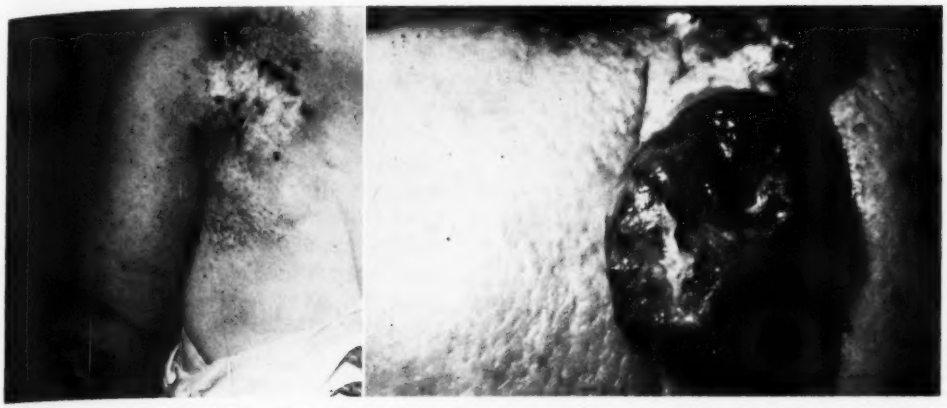
CASE IV: B. K., a 51-year-old nurse, neglected a large tumor in the right breast for over six months. When she consulted a surgeon, there were large supraclavicular nodes and a larger mass in the right axilla with massive edema and stiffness of the arm. The condition was inoperable.

Deep roentgen therapy was administered to the right breast, right axilla, and right supraclavicular area. The tumor in the breast and axilla, as well as the supraclavicular nodes, decreased markedly in size, but no appreciable change occurred in the edema of the right upper extremity. There was no roentgen or clinical evidence of metastases in the lungs or skeletal structures.

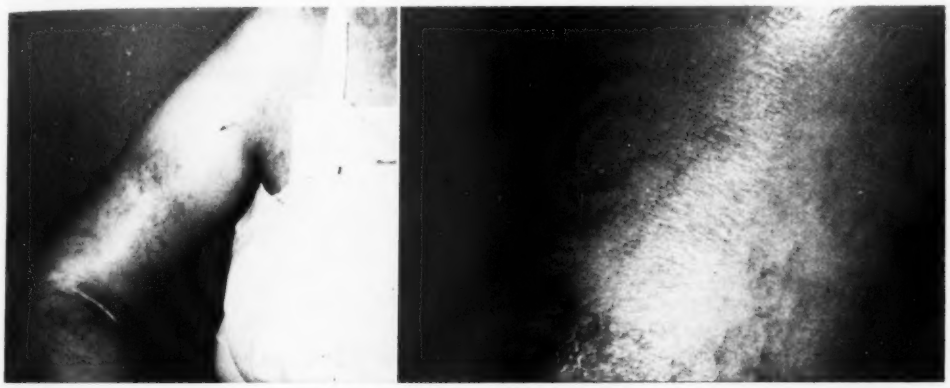
The tissues of the right arm became more tense, and within two months there was an area of purplish discoloration with induration and telangiectasis of the distal half of the upper arm (Figs. 8 and 9). Clinically, the appearance was quite characteristic of lymphangiosarcoma, with changes closely resembling those seen in our other patients. Radical amputation and/or further roentgen therapy was refused by the patient. A biopsy was not obtained in this case which was included because of the typical clinical picture. The patient died approximately seven months after the recognition of her disease.

TREATMENT

No single therapeutic measure has proved satisfactory in lymphangiosarcoma



Figs. 6 and 7. Case III. Edematous arm for sixteen years after mastectomy. The tumor nodules have spread from the forearm to the axilla and anterior chest wall. They were at first diagnosed as recurrent carcinoma from the breast. Fig. 7 (to the right) is a close-up of the ulcerating nodules of the forearm.



Figs. 8 and 9. Case IV. Lymphedematous arm for less than one year shows purplish discoloration with induration and telangiectasis so characteristic of early lymphangiosarcoma. Fig. 9 (to the right) is a close-up of the telangiectasis on the medial aspect of the upper arm.

in the edematous arm, and, from the small number of cases reported, it is difficult to evaluate any single method of treatment as being better than another. In some instances, good immediate clinical regression of the tumor has been achieved with irradiation, and it is suggested, therefore, that energetic radiotherapy, covering wide fields, be the initial form of treatment. Intrascapulothoracic amputation should be considered if a favorable response is not obtained within a relatively short time after the institution of irradiation. This is a formidable procedure, both physically and psychologically, and the patient will not be quick to accept a forequarter amputation or shoulder disarticulation. Radical surgery has not proved curative in the reported cases. The ineffectiveness of this form of treatment may be attributed to the delay in diagnosis of the disease and to its early dissemination.

Chemotherapy may prove effective in the control or possibly in the cure of the disease. Fry *et al.* (1959, 1960) administered triethylene thiophosphoramide to 2 patients with lymphangiosarcoma. In 1, there was no apparent change in the tumor growth. The second patient, who had roentgen evidence of pulmonary metastases, died of cardiac failure eleven months after chemotherapy. At autopsy, very little

tumor was found in the areas of pulmonary metastases. This finding was interpreted by the pathologist as due to necrosis of tumor, most likely secondary to the triethylene thiophosphoramide.

DISCUSSION

Chronic lymphatic obstruction appears to be an overwhelming common factor in all reported cases of lymphangiosarcoma. The cause of the lymphedema in the extremity is still unknown, but radical mastectomy can certainly be considered an etiologic agent. It would seem likely that there is a relationship between long-standing lymphedema and lymphangiosarcoma.

Nine cases in which lymphangiosarcoma developed in a lymphedematous extremity in the absence of any previous malignant disease have been reported in the literature and were summarized by McConnell and Haslam. This would tend to rule out the possibility that a general systemic carcinogen is the etiologic agent, as was postulated by Stewart and Treves in their original report of the disease.

Martorell (1951) called attention to the fact that lymphedema, as opposed to venous edema, excites fibroblastic proliferation and possibly neoplasia. He advanced the theory that stagnant lymph may be the origin of the proliferation of lymphatic endothelia and lead to the formation of multiple nodular tumors of angiosarcomatous structure.

Treves (1957), after review of the incidence of lymphedema in 3,013 cases of carcinoma of the breast treated with radical mastectomy, wrote: "The most striking factor associated with post-mastectomy swollen arm was irradiation." It is not an essential factor, however, for 1 of the cases in our group did not receive previous postoperative therapy, and 19 of the 34 recorded cases to date had not been given any form of roentgen irradiation.

Some authors have likened the histologic pattern of lymphangiosarcoma to certain phases of Kaposi's sarcoma, which occurs predominantly in the lower extremity of males. Many histologic features are common to both conditions, as was pointed out in the initial study of Stewart and Treves. They concluded, however, that the neoplasm specifically originated in the lymphatics and should be considered distinct from angiosarcoma.

McConnell and Haslam (1959) made an excellent histologic study of the tumor and have divided its course of development into three stages.

"*Stage 1: Prolonged Lymphoedema.*— The essential feature . . . is a widespread oedema and degeneration of the collagen tissue and fat in the dermis and subcutaneous tissue. . . .

"*Stage 2: Pre-malignant Angiomatosis.* — The characteristic change in this stage is a proliferation of small vessels in the dermis and subcutaneous tissue in numerous foci throughout the arm . . . . Many of these proliferating vessels appear to be arising from lymphatics, but others were filled with red corpuscles and were presumably arising from blood capillaries . . . . The more superficial areas are manifest on the surface as bruises or vesicles . . . . The proliferating vessels are frequently accompanied by lymphocytic infiltration . . . . The more advanced lesions show what must be considered as early malignant changes, with mitotic figures and cellular pleomorphism. . . .

"*Stage 3: Frankly Malignant Angiosarcoma.*—These tumors . . . arise multifocally from areas of premalignant angiomatosis. . . . Bizarre vascular channels, lined by pleomorphic malignant endothelial cells, frequently containing red corpuscles, infiltrate the adjacent tissue. At the other end (of the scale) . . . the tumour consists of (*a*) spindle cells with deeply staining nuclei and scanty cytoplasm. . . ."

SUMMARY

The prognosis for patients with lymphangiosarcoma in the lymphedematous arm following mastectomy is grave, and most of them die from pulmonary metas-

tases within a year. Prompt diagnosis by recognition of early skin changes, namely, yellowish discoloration of the skin with induration, purplish-red blotches simulating a "bruise" or ecchymosis, areas of patchy telangiectasis, should be followed by immediate biopsy and intensive therapeutic measures.

Radical radiation therapy or radical amputation is thought to be the best method of treatment. It is hoped that some day isolation perfusion technic may control the disease or that it may be cured by a chemotherapeutic agent.

Radiologists and surgeons who are actively engaged in the follow-up care of post-mastectomy patients should constantly be on the alert for the early signs of lymphangiosarcoma in the lymphedematous arm.

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REFERENCES

AIRD, I., WEINBREN, K., AND WALTER, L.: Angiosarcoma in a Limb the Seat of Spontaneous Lymphœdema. Brit. J. Cancer **10:** 424–430, September 1956.

BOWERS, W. F., SCHEAR, E. W., AND LEGOLVAN, P. C.: Lymphangiosarcoma in the Postmastectomy Lymphedematous Arm. Am. J. Surg. **90:** 682–686, October 1955.

BIRGE, R. F., PEISEN, C. J., THORNTON, F. E., AND POWELL, L. D.: Angiosarcoma in Postmastectomy Lymphedema. J. Iowa M. Soc. **47:** 491–495, August 1957.

CRUSE, R., FISHER, W. C., III, AND USHER, F. C.: Lymphangiosarcoma in Postmastectomy Lymphedema: A Case. Surgery **30:** 565–569, September 1951.

DOREMUS, W. P., AND SALVIA, G. A.: Lymphangiosarcoma in the Postmastectomy Lymphedematous Arm. Am. J. Surg. **96:** 576–579, October 1958.

FERRARO, L. R.: Lymphangiosarcoma in Postmastectomy Lymphedema: A Case Report. Cancer **3:** 511–514, May 1950.

FROIO, G. F., AND KIRKLAND, W. G.: Lymphangiosarcoma in Post-Mastectomy Lymphedema. Ann. Surg. **135:** 421–425, March 1952.

FRY, W. J., CAMPBELL, D. A., AND COLLER, F. A.: Lymphangiosarcoma in Postmastectomy Lymphedematous Arm. Arch. Surg. **79:** 440–446, September 1959.

FRY, W. J.: Personal communication, 1960.

HALL-SMITH, S. P., AND HABER, H.: Lymphangiosarcoma in Postmastectomy Lymphœdema (Stewart-Treves Syndrome). Proc. Roy. Soc. Med. **47:** 174–175, March 1954.

HERRMANN, J. B., AND GRUHN, J. G.: Lymphangiosarcoma Secondary to Chronic Lymphedema. Surg., Gynec. & Obst. **105:** 665–674, December 1957.

HILFINGER, M. F., JR., AND EBERLE, R. D.: Lymphangiosarcoma in Postmastectomy Lymphedema. Cancer **6:** 1192–1199, November 1953.

HOPE-STONE, H. F., AND BENCE, E. A.: Lymphangiosarcoma Occurring in Association with Lymphœdema. J. Fac. Radiologists **10:** 73–76, April 1959.

JESSNER, M., ZAK, F. G., AND REIN, C. R.: Angiosarcoma in Postmastectomy Lymphedema (Stewart-Treves Syndrome). Arch. Dermat. & Syph. **65:** 123–129, February 1952.

KETTLE, J. H.: Lymphangiosarcoma Following Post-Mastectomy Lymphœdema. Brit. M. J. **1:** 193–194, Jan. 26, 1957.

MCCARTHY, W. D., AND PACK, G. T.: Malignant Blood Vessel Tumors. Report of 56 Cases of Angiosarcoma and Kaposi's Sarcoma. Surg., Gynec. & Obst. **91:** 465–482, October 1950.

MCCONNELL, E. M., AND HASLAM, P.: Angiosarcoma in Post-mastectomy Lymphœdema. A Report of 5 Cases and a Review of the Literature. Brit. J. Surg. **46:** 322–332, January 1959.

MARSHALL, J. F.: Lymphangiosarcoma of Arm Following Radical Mastectomy. Ann. Surg. **142:** 871–874, November 1955.

MARTORELL, F.: Tumorigenic Lymphedema. Angiology **2:** 386–392, October 1951.

NELSON, W. R., AND MORFIT, H. M.: Lymphangiosarcoma in the Lymphedematous Arm after Radical Mastectomy. Cancer **9:** 1189–1194, November-December 1956.

PATTON, R. J.: Lymphangiosarcoma: Late Complication of Mastectomy. Illinois M. J. **114:** 286–288, December 1958.

RAVEN, R. W., AND CHRISTIE, A. C.: Hæmangiosarcoma: Case with Lymphatic and Hæmatogenous Metastases. Brit. J. Surg. **41:** 483–489, March 1954.

RAWSON, A. J., AND FRANK, J. L., JR.: Treatment by Irradiation of Lymphangiosarcoma in Postmastectomy Lymphedema: Report of a Case. Cancer **6:** 269–272, March 1953.

SOUTHWICK, H. W., AND SLAUGHTER, D. P.: Lymphangiosarcoma in Postmastectomy Lymphedema; Five-Year Survival with Irradiation Treatment. Cancer **8:** 158–160, January-February 1955.

STEWART, F. W., AND TREVES, N.: Lymphangiosarcoma in Postmastectomy Lymphedema. A Report of 6 Cases in Elephantiasis Chirurgica. Cancer **1:** 64–81, May 1948.

TREVES, N.: An Evaluation of the Etiological Factors of Lymphedema Following Radical Mastectomy: An Analysis of 1,007 Cases. Cancer **10:** 444–459, May-June 1957.

(Pro le summario in interlingua, vider le pagina sequente)

SUMMARIO IN INTERLINGUA

Lymphangiosarcoma in Bracios Lymphedematose post Mastectomia

Un altemente maligne lymphangiosarcoma pote disveloppar se in un bracio que es chronicamente edematose post mastectomia radical pro carcinoma mammari. Quatro tal casos es describite.

In general, le lymphedema ha essite presente depost sex annos o plus quando un vagemente purpuro-rubie lesion macular subdermal comencia manifestar se. Isto se allarga con un discoloration profunde. Simile areas satellitic de discoloration se disveloppa e deveni confluente, con le formation de tumores bullose o papillomatose. Metastases pulmonar es de occurrentia precoce.

Nulle specific mesura therapeutic individual se ha provate satisfactori. Es proponite que un radiotherapia energic debe esser usate como forma initial de tractamento. Amputation intrascapulothoracic debe esser considerate si nulle favorabile responsa es obtenite intra un relativemente breve intervallo de tempore. Chimotherapia pote esser de valor.

Chronic obstruction lymphatic pare esser un factor irresistibile in omne le reportate casos de lymphangiosarcoma. Il pare esser probabile que il existe un relation inter lymphedema de longe duration e lymphangiosarcoma. Le prognose es grave. Le majoritate del patientes mori intra un anno ab metastases pulmonar.

Steroids and the Skeleton[1]

R. O. MURRAY, M.B.E., M.D., M.R.C.P.E., D.M.R.

HARVEY CUSHING in 1932 first described the syndrome of obesity, hypertension, weakness, and depression of sexual function which has since become classically designated by his name. The condition was attributed by him to overproduction of pituitary adrenocorticotrophic hormone in association with the presence of a basophil adenoma. Although he postulated that the consequent stimulation of the adrenal cortex resulted in endogenous overproduction of the adrenocortical steroids, it has since been shown, largely as a result of the work of Albright, Parson, and Bloomberg (1941), that the presence of such an adenoma is not essential for the development of the syndrome. Primary disease of the adrenal cortex itself, either simple hyperplasia or benign or malignant neoplasia, is the more common cause, without stimulus from the pituitary. The hormones responsible for the skeletal changes in this condition are cortisone and hydrocortisone. During the last decade, these substances and similar steroids have been made available for therapeutic use and a number of instances of iatrogenic disease have resulted from their employment. These untoward sequelae are relatively uncommon, and individual radiologists may not encounter personally all the varieties that may occur. That such therapy may result in fully developed Cushing's syndrome, with its principal skeletal manifestations of osteoporosis, pathological fractures, and abnormal callus formation, is now well recognised. Study of the literature, however, indicates that certain lesser changes may be observed, particularly in connection with intra-articular injections. Diminution of pain sense and suppression of inflammatory reaction as a result of a surfeit of these hormones, whether natural or therapeutic, may cause the diagnosis of such lesions to be delayed.

RADIOLOGICAL CHANGES IN THE SKELETON IN CUSHING'S SYNDROME

(*a*) *Osteoporosis:* The generalised increase of translucency affecting the bony structures in the majority of patients suffering from Cushing's syndrome results from inability to lay down the osteoid tissue or protein matrix, which is an essential preliminary to the formation of new bone. Such bone as is present is normally calcified. This condition, therefore, is a true example of osteoporosis. In a minority of patients, and in early cases, no radiological bone abnormality can be detected. When only minimal changes of osteoporosis are present, differentiation on radiological grounds from osteoporosis of other origin cannot be made. Cushing recognised osteoporosis as a fundamental feature of the syndrome and this observation was confirmed by Eisenhardt and Thompson (1939) and by Sussman and Copleman (1942).

The condition is usually first visible in the spine, where a fine, vertical linear striation becomes apparent, with consequent prominence of the vertebral plates. The skull, ribs, and pelvis become similarly affected. Although earlier reports suggested that the appendicular skeleton was exempt from this process, it is in fact also involved, but such changes may at first be obscured by the relative density of the long bones.

(*b*) *Pathological Fractures:* A natural corollary to the osteoporotic process is the relative fragility of the weakened bony structures and the occurrence of pathological fractures, with which a history of trauma may be slight or even entirely absent. The lower dorsal and upper

[1] From the Institute of Orthopaedics and Royal National Orthopaedic Hospital, London, England. Presented at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960.

lumbar vertebral bodies are particularly susceptible. According to the severity of the lesion the appearance may vary from a minimal infraction to multiple and severe collapse, which, with the expansion of the intervening intervertebral discs, causes a "fish vertebrae" deformity. The ribs are also commonly involved and, although such fractures may take place at any point within the costal arch, widening of the anterior ends is frequently visible. This was observed by Sussman and Copleman and came to be sought as a diagnostic feature. Although these authors were unable to detect any definite fracture lines in connection with the lesions, it is now considered that the appearance in fact results from multiple infractions. Fractures of the pubic and ischial rami are not uncommon, and Wang and Robbins (1956) have reported their occurrence in long bones.

(*c*) *Abnormal "callus" formation* becomes visible around these fractures. Although it is often exuberant in quantity, it tends to be less well defined than that seen in the repair of fractures of normal bone. It was described by Sosman (1949) and again by Wang and Robbins, who applied to it the descriptive term "cotton-wool." Dent (1955) has pointed out that, in contrast, the rib fractures which are frequently evident in idiopathic osteoporosis heal with minimum callus formation. Sosman had commented on an unusual increase of density of vertebral plates which occurred with crush fractures of vertebral bodies. Howland, Pugh, and Sprague investigated this point by comparing the spinal radiographs of 69 patients suffering from Cushing's syndrome with those of 50 patients having severe osteoporosis of other origin. Whereas more than half of the former group showed this sign, which these workers termed "marginal vertebral condensation," it was observed in only one patient of the control series. It was considered that this phenomenon might well be associated with abundant osteoid, of the same type as that seen around fractures of other bones in Cushing's syndrome. In a previous paper (Murray 1960) it was suggested that these changes represented only an incomplete and abortive attempt at the healing process, the opacity being due to a pathological deposition of calcium. This took place within abnormal cartilage which formed in association with partial inhibition of osteoblastic function. The term *pseudo-callus*, by analogy with the term pseudo-fracture employed in osteomalacia, was proposed. Nevertheless, healing cannot fail completely, since residual deformities of old united fractures may be visible when the disease is of long standing.

(*d*) *Delay in Skeletal Development.* This feature of the syndrome has not attracted great attention, but references to individual examples have been made by several authors, as Freyberg and Grant (1936), Eisenhardt and Thompson, Sosman, Follis (1951), and Howland *et al.* It is possible that the number of child subjects is too small for such retardation commonly to be recognised, especially as a malignant neoplasm is the more usual cause of the disease in the first decade. Death may therefore ensue before such delay becomes a notable feature.

CLINICAL ASPECTS

In conjunction with the radiologic findings, reference must be made to two clinical aspects of the disease which are of great importance.

(*a*) *Suppression of Pain Sense:* Many of the fractures which take place in Cushing's syndrome are only incidentally discovered in the course of radiological investigation, because the normal warning sense of pain has been diminished or, indeed, has been entirely absent. This peculiar anaesthesia was first noted by Sussman and Copleman in 1942. In this connection the work of Howland *et al.* is particularly interesting. Six patients with fractures of the pubic or ischial rami were all asymptomatic; of 55 patients with rib fractures, of whom 32 had an average of over six fractures each, only 3 reported chest pain. On the other hand, of 33 pa-

tients with fractures of vertebral bodies, all but 5 complained of back pain. With such spinal fractures the pain is often of a girdle type, and it appears possible that this anomalous occurrence of pain may be attributable to mechanical nerve root pressure rather than to the fractures themselves.

(*b*) *Masking of Infections:* Of the 12 patients in Cushing's original series, 2 alone survived, and 1 of these nearly succumbed to widespread lumbar abscesses. Infection was the immediate cause of death in 6 of the 10 fatal cases and appears to have been a contributory factor in 2 others. Sosman in 1949 stressed that these patients stood operation poorly and were apt to die of uncontrollable infection after operation or injury. The first signs of infection, therefore, may be radiological rather than clinical.

FUNCTIONS OF THE ADRENOCORTICAL STEROIDS

A brief review of the functions of the adrenocortical steroids is of value in clarifying the mechanisms whereby develop the changes so far described.

The hormones produced by the adrenal cortex have two main types of function. The first, mineralo-corticoid activity, is associated with sodium and potassium metabolism and hence water retention. The second, gluco-corticoid activity, among other effects, particularly influences the skeleton. The adrenocorticotrophic hormone of the anterior pituitary stimulates the adrenal cortex to activate these functions to approximately equal degree. Hyperfunction of the adrenal cortex may be due to increased stimulation by excess ACTH but more commonly results from hyperplasia or neoplasia of the cortex itself.

Gluco-corticoid activity is largely produced by the hormones cortisone and hydrocortisone, which have the following effects on the skeleton.

(*a*) *The anti-anabolic effect* reduces protein synthesis, including that derived from osteoblastic function, so that the formation of bone matrix is diminished. Sissons (1956) has demonstrated that normal bone resorption in the presence of osteoclasts nevertheless continues. Thinning of the trabeculae and consequent weakening of the bony structures renders them peculiarly liable to fractures in the presence of minor stresses and strains.

Experimental studies in animals by Sissons and Hadfield (1951) and by Duthie and Barker (1955), with these hormones, have also led to the conclusion that the pseudo-callus demonstrated radiographically is due to partial inhibition of the normal process of fracture repair. Similarly, Storey (1957, 1958) demonstrated delay in skeletal development in rabbits, thus confirming the clinical observations of the same nature made in a large series of children by Blodgett *et al.* (1956).

The anti-anabolic effect therefore provides a satisfactory explanation for the development of the osteoporosis, the consequent fractures, the pseudo-callus formation, and partial inhibition of skeletal development, which are the main radiologic features of bone involvement in Cushing's syndrome.

(*b*) *The antitoxic effect* is associated with masking of symptoms, explaining the diminution or, indeed, complete suppression of painful response to fractures.

(*c*) *The anti-inflammatory effect* diminishes the natural protective response to infections, so that these are liable to develop in a dangerous manner, with suppression of pain as a symptom, causing them easily to be overlooked.

CASE I: *Cushing's Syndrome; Adrenal Hyperplasia* (By courtesy of Dr. Rohan Williams). A 26-year-old woman gave a history of illness beginning at the age of nine with progressive development of hypertension, abnormal increase of weight, ankle oedema, and abdominal striae. Growth was stunted and ceased at fifteen. Menstruation was completely suppressed until the age of twenty. On admission, the urinary 17-ketosteroid level was abnormally high and a marked dorsal kyphos was noted. Symptoms and signs regressed after bilateral total adrenalectomy, except for skeletal deformity, and the patient was satisfactorily maintained on cortisone.

The preoperative radiographs showed typical changes. Osteoporosis of a generalised and severe type was present. Pathological fractures in large

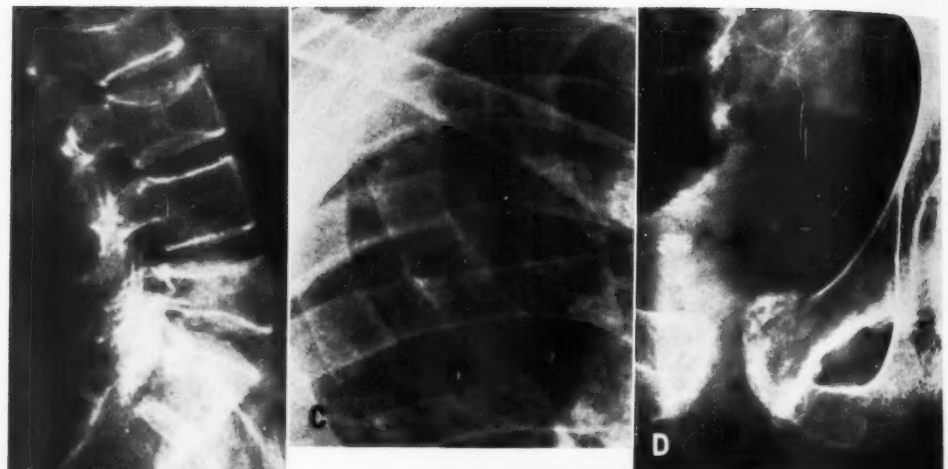

Fig. 1. Case I: Cushing's syndrome; adrenal hyperplasia.

A. Generalised osteoporosis present with multiple vertebral crush fractures. Marginal condensation visible in upper tables of L2 and L5.

B. Multiple rib fractures and infractions. Residual widening of anterior ends of right fifth and sixth, and left fourth ribs. Cardiac enlargement.

C. Irregular pseudo-callus around fractures of right second rib. Bony structures are very osteoporotic.

D. Fractures of left pubic rami close to symphysis pubis, with pseudo-callus formation.

E. Delayed closure of iliac apophyses. Generalised osteoporosis.

From Murray: Brit. J. Radiol. **33**: 1–19, 1960.

numbers were demonstrated, ranging from a minimal infraction of the fourth lumbar vertebra to severe collapse of the mid-dorsal vertebral bodies, which had assumed a biconcave appearance of "fish vertebrae," with considerable resultant kyphosis. Some evidence of marginal vertebral condensation, as described by Howland *et al.* (1958), could be discerned in the upper tables of the first, second, and fifth lumbar vertebral bodies (Fig. 1, A). The ribs had suffered many fractures and infractions. Some of these had united, leaving residual deformity. Widening of the anterior ends of several ribs, notably the right fifth and sixth, and the left fourth, was demonstrated. These deformities, as indicated above, had undoubtedly resulted from old, healed infractions. Cardiac enlargement was incidentally visible, attributable to the associated hypertension (Fig. 1, B). A photographic enlargement of the right upper chest shows two fractures of the right second rib, each surrounded by irregular and poorly defined calcification. This is the *pseudo-callus* to which reference has been made (Fig. 1, C). Fractures of the left ischial pubic rami close to the symphysis pubis had provoked a similar response (Fig. 1, D). The film of the pelvis (Fig. 1, E) showed failure of the iliac apophyses to close. Wide extremes for the fusion of these apophyses have been quoted in the literature, but Zaoussis and James (1958), in an assessment of 234 patients, showed this to occur in females between the ages of thirteen and a half and twenty-three and a half years. The patency of these apophyses at the age of twenty-six years can therefore be regarded as reasonable evidence of delayed skeletal development. It is of considerable interest that, despite the numerous fractures demon-

strated in this patient, pain was not a presenting feature.

RADIOLOGICAL CHANGES IN THE SKELETON WITH ORAL ADRENOCORTICAL STEROID THERAPY

Research into the function of the adrenal cortex proceeded vigorously from the time of Cushing's original description to reach a climax on Sept. 21, 1948. On that day Hench, Kendall, Slocumb, and Polley (1949) administered for the first time a dose of 100 mg. of their compound "E," subsequently renamed cortisone, to a young woman suffering from rheumatoid arthritis. Its miraculously beneficial action attracted the attention of the medical world and, since then, this substance and other adrenocortical steroids have been investigated in the treatment of almost every known malady. Warnings that the new weapon was two-edged began to appear as early as 1950, when Sprague *et al.* (1950) reported the development of typical Cushing's syndrome in patients receiving this therapy. As the years progressed, more and more reports of iatrogenic changes appeared in the international literature, the majority from the United States (Boland and Headley, 1950; Graham, 1950; Steinbrocker *et al.*, 1951; Boland, 1951; Margolis and Caplan, 1951; Demartini, Grokoest, and Ragan, 1952; Soffer and Bader, 1952; Teicher and Nelson, 1952; de Sèze, Hubault, and Renier, 1953; Curtiss, Clark, and Herndon, 1954; Luder, 1954; Eisenstadt and Cohen, 1955; Ansell, 1958).

It is now known that oral steroid therapy may produce all the changes in the skeleton which have previously been recognised in connection with the development of Cushing's syndrome of natural origin. The period and quantity of such treatment necessary to cause these iatrogenic complications may show considerable variation. The cortisone or cortisone-equivalent dosage has usually been of the order of 50 to 100 mg. a day, and the more severe manifestations have usually developed during periods of continuous therapy varying between nine and eighteen months. Lesser manifestations, however, have often been reported after much shorter periods and after a relatively small total dosage.

Osteoporosis, if the technical difficulties of its demonstration can be overcome, is usually the presenting radiological sign, but it may not be observed until a fracture is suspected clinically.

The primary condition for which steroid therapy has been given is, in the vast majority of reported cases, rheumatoid arthritis. Nevertheless, these complications have also arisen in patients for whom the indication for treatment has been quite different. This is of importance in refuting suggestions that the development of osteoporosis may simply be an extension of the rheumatoid process. In that condition osteoporosis tends to be para-articular in distribution and the spine is usually exempt. Some authors (Sprague *et al.*, 1950; de Sèze *et al.*, 1953; Eisenstadt and Cohen, 1955) have referred to the value of androgens and oestrogens in minimising the development of osteoporosis. De Sèze also suggested the use of ascorbic acid, and Luder (1954) advocated ambulation and the stimulus of active use to achieve this effect.

Pathological fractures may occur as a relatively early complication. Boland, Demartini, Luder, and Steinbrocker all reported examples occurring within five to eight weeks after therapy was begun. The thoracolumbar region of the spine is again the most common site, but a number of other regions have been affected, including the femoral neck, ribs, and pelvis. The rate of repair of such fractures has been the subject of very little comment, but de Sèze noted delay in the appearance of healing. These fractures show the same *pseudo-callus formation* as has been noted in connection with Cushing's syndrome of natural origin. They appear to occur more frequently in patients with rheumatoid arthritis who have received steroid therapy than in those who have not. Baer (1941), in a series of 1,625 cases of arthritis, noted only 14 fractures

in the rheumatoid group, of which only one affected the spine. Badley and Ansell (1960), however, observed a much higher incidence in a group of 216 child patients, of whom 63 had received steroid therapy. In the latter group there was a significantly higher incidence of vertebral fractures and a considerably lower incidence of pain as a presenting symptom.

Delay in skeletal development may be expected in children, as has been shown by the work of Blodgett *et al.*

Mechanical degeneration of joints is a particularly important radiological appearance in iatrogenic disease of this type. It is surprising that no counterpart to such changes has been found in the literature of Cushing's syndrome of natural origin, since it is difficult to believe that this is a genuine variant.

Pietrogrande and Mastromarino (1957) reported severe degenerative changes in a hip in a patient with iatrogenic Cushing's syndrome. The radiological findings were comparable to those of a Charcot neuropathy. Further examples have been reported by Ansell (1958), Murray (1960), and Sweetnam, Mason, and Murray (1960). The majority of these have involved the hips, but such changes have also been observed in the metacarpophalangeal joints and ankles with oral therapy. Reference will be made later to similar effects on the hips and knees with intra-articular injection of steroids. The process of disintegration may take between twelve and twenty-four months to develop. It appears to be caused by avascular necrosis associated with pathological infractions and collapse, particularly of weight-bearing articular surfaces. Pre-existing joint damage due to rheumatoid arthritis or osteoarthritis has often been present. The enormous force transmitted through the femoral head makes the hip joint particularly susceptible to such damage when the bony structures are abnormally fragile and the protective sense of pain is removed. The ultimate degree of joint disorganisation can barely be distinguished radiologically from a neuropathy.

Infections of bones and joints, whether latent before the commencement of therapy or acquired at a subsequent stage, may spread silently and at an alarming rate with the production only of unduly mild symptoms and signs. Mills, Boylston, Greene, and Moyer (1957) reported 2 cases of joint infection during oral steroid therapy, in both of which pain and fever were marked by their absence. Similar observations were made by Ansell (1958) and by Murray (1960). In such cases the infection almost always involves a joint with rapid development of destructive changes, which may be accompanied by radiological evidence of abscess formation. Relatively little reactive sclerosis occurs, and the radiological picture may suggest a tuberculous arthritis of an unusually rapid and progressive type. Some such lesions, however, have been shown pathologically to be, in fact, pyogenic in origin.

Even radiological diagnosis may on occasion prove inadequate. Steiner (1958), in a personal communication, stated that he had encountered a number of patients in whom Cushing's syndrome developed on prolonged cortisone therapy, 100 mg. a day. Two of these were women in the third decade, who suffered from lupus erythematosus. Both patients died, and postmortem examination revealed the presence of multiple infective lesions in the spine, which had been completely asymptomatic during life and could not be identified on review of the radiographs.

The danger of infection with steroid therapy has probably not yet been fully appreciated, and knowledge of the analgesic effects of the steroids on lesions of bones and joints should possibly be more widespread. The history of Cushing's original series should, perhaps, have provided the first warnings, but since his original description it has become infinitely more easy to abort infections by antibiotic drugs, provided their existence has been recognised.

Clinical Aspects

Joint degenerations appear to be attributable to suppression of the warning

sense of pain. An annotation on the subject of side-effects on the skeleton from steroid therapy was published in the *British Medical Journal* in 1955. The suppression of pain was at that time already under suspicion as a prime factor in the development of other complications with this therapy and reference was made to an "increased sense of well-being, leading to unaccustomed activity."

Charcot (1868), in his original description of neuropathies, attributed the absence of pain in these severe disorders to joint anaesthesia, noting that they occurred in locomotor ataxia and were not associated with inflammation. Eloesser (1917) convincingly demonstrated that such lesions resulted from trauma, when the warning sense of pain could not be appreciated. He obtained experimental proof by sectioning posterior nerve roots leading to a particular extremity in cats. Typical neuropathies subsequently developed in the desensitised joints. Among the numerous causes of this sensory interference, neurosyphilis, syringomyelia, and spina bifida are perhaps the best known. Local inhibition of pain sense, therefore, in the condition under consideration, accounts reasonably for the avascular necrosis and joint degeneration which have been observed.

It should be appreciated that osteoarthritic joints, particularly the hips, may undergo very severe degenerative changes without steroid therapy ever having been given. Such changes may well approach the appearances which have been described, but the period necessary for their development is longer, often years rather than months. Clinical differentiation is made easy by a history of progressive pain and disability. In a review of radiographs of such patients in this hospital it has not been possible to find a truly comparable example.

Infections: The relatively asymptomatic development of infective lesions can be explained by the combination of a failure of the body to mobilize its normal defences and, once again, the suppression of the warning sense of pain.

CASE II: *Iatrogenic Cushing's Syndrome; Rheumatoid Arthritis* (By courtesy of Dr. F. H. Stevenson). This patient was a woman of 65. In June 1953, when she was 62, rapidly progressive rheumatoid arthritis had developed, which failed to respond to gold and butazolidine therapy. From October 1953, 75 mg. cortisone daily was given for five months, still without relief; it was then discontinued owing to the occurrence of ankle oedema. The condition, however, deteriorated further and after a few weeks ACTH, 20 i.u. daily, was given for a period of two months, greatly relieving the symptoms. At the same time testosterone was administered in an attempt to prevent the complication of Cushing's syndrome. The steroids on this occasion had to be discontinued owing to a staphylococcal pneumonia. In September 1955, Cushing's syndrome had developed, with the following radiological changes.

In the chest (Fig. 2, A) generalised osteoporosis was present, with numerous fractures and infractions of the ribs, around some of which pseudo-callus formation was visible. A residual lung abscess was also evident in the left lower zone. This was virtually asymptomatic and had remained unhealed since the attack of pneumonia, incidentally illustrating the anti-inflammatory effect in lung tissue. A small right basal pleural effusion was also present. (Such effusions, either in the pleura or the pericardium, may occur in Cushing's syndrome as a result of interference by mineralo-corticoid function of the hormones with sodium and potassium metabolism.) Osteoporosis, with multiple compression fractures, was shown in the dorsal spine, with the sign of marginal condensation in the upper tables of the bodies of D8 and D9 (Fig. 2, B). The pelvis also showed generalised osteoporosis, with a stress fracture in the left femoral neck (Fig. 2, C). All the fractures were asymptomatic.

CASE III: *Iatrogenic Cushing's Syndrome; Rheumatoid Arthritis* (By courtesy of Mr. J. D. Wilson). A woman of 36 years suffered from widespread and painful rheumatoid arthritis. In October 1956, steroid therapy was initiated with prednisone, 15 mg. daily. Pain was reduced but not completely relieved. The patient declared herself unable to do without this therapy, and by November 1958 she displayed typical clinical evidence of Cushing's syndrome. Radiologic examination of the pelvis showed widespread osteoporosis with changes of rheumatoid arthritis in the right hip (Fig. 3, A). Similar osteoporosis was visible in the spine, with a minor crush fracture of the body of D7 (Fig. 3, B).

The patient was subsequently admitted to the hospital in an attempt to wean her from steroid therapy. This completely failed, since withdrawal of steroids was followed by severe increase of pain. In June 1959, the right hip was manipulated under anaesthesia. The hip was subsequently mobile and, although the patient still complained of pain, this

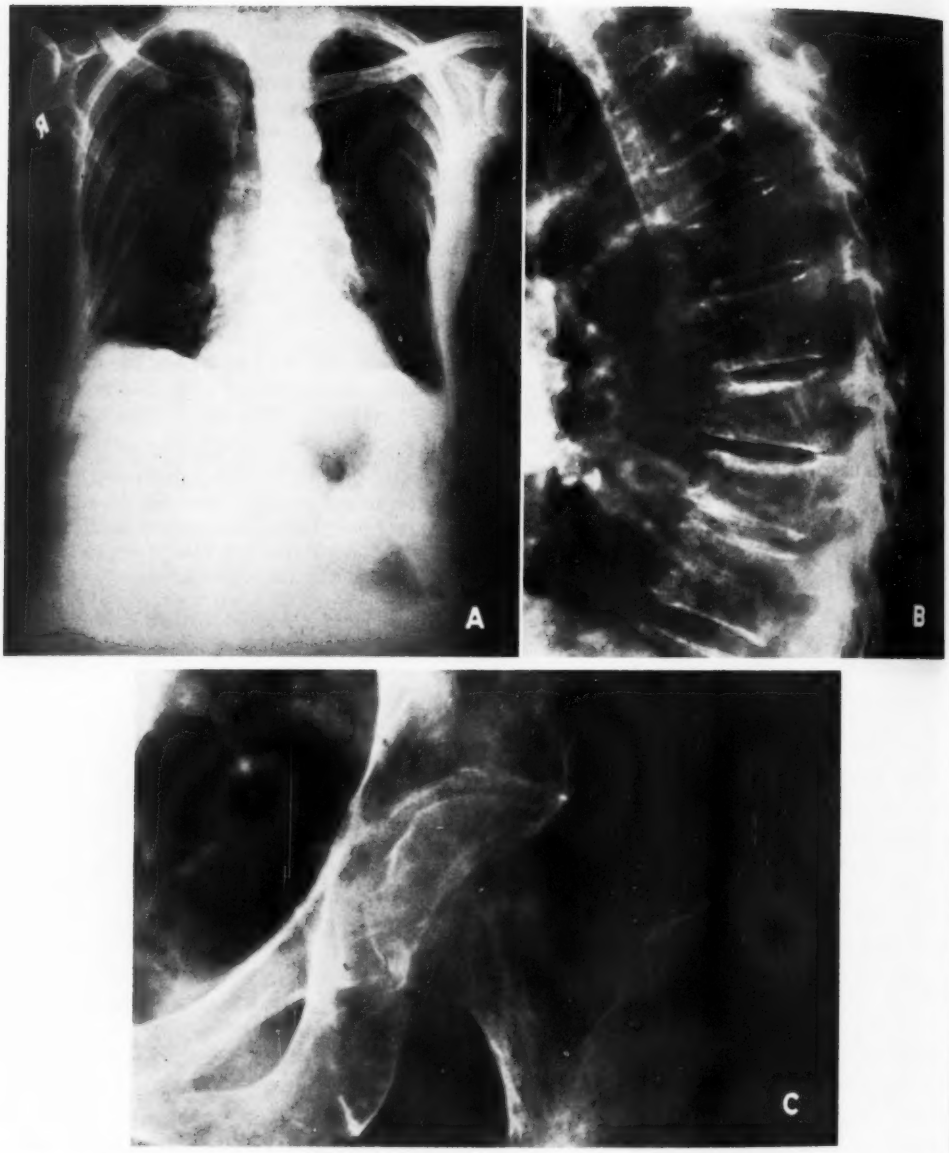

Fig. 2. Case II: Iatrogenic Cushing's syndrome; rheumatoid arthritis.
A. Multiple fractures and infractions of ribs, some with a little pseudo-callus formation. Generalised osteoporosis. Unresolved pneumonic consolidation in left lower zone, surrounding a residual lung abscess.
B. Generalised osteoporosis with multiple vertebral collapse. The upper tables of the bodies of D8 and D9 show marginal condensation.
C. Asymptomatic stress fracture of left femoral neck. Severe generalised osteoporosis.
From Murray: Brit. J. Radiol. **33**: 1–19, 1960.

was not accentuated until about a fortnight after the procedure. Pain then increased and after a month radiological examination of the right hip showed that the femoral neck had suffered a fracture, with considerable absorption of bone on either side of it (Fig. 3, C). It appears likely that this fracture occurred primarily during manipulation and it is interesting that no immediate pain from this cause was reported. It is possible that the fracture was originally of the stress type and had

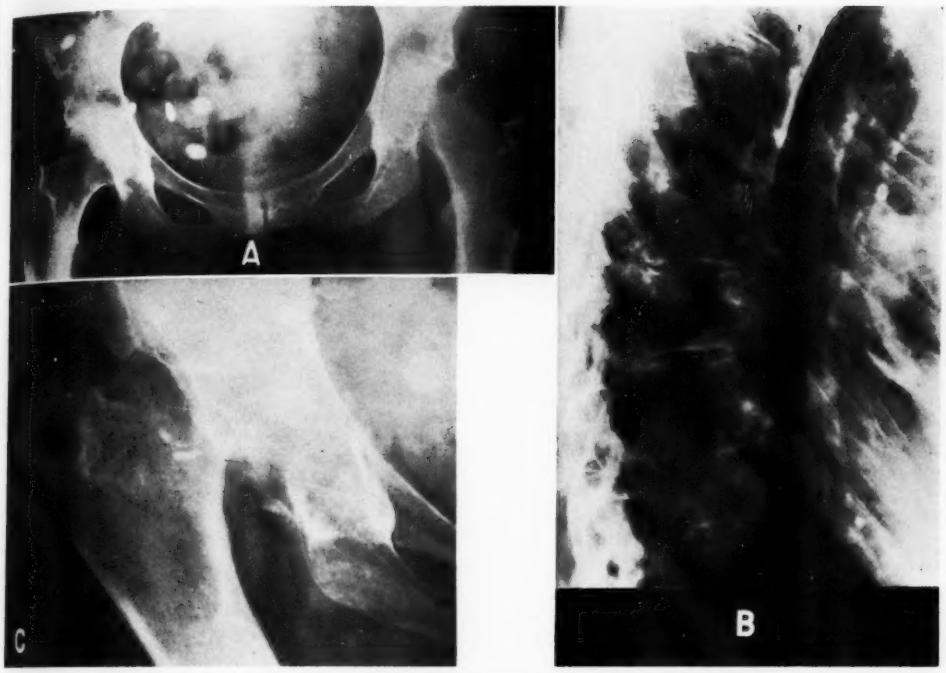

Fig. 3. Case III: Iatrogenic Cushing's syndrome: rheumatoid arthritis.
A. Osteoporosis of pelvis with rheumatoid arthritis of right hip.
B. Minor crush fracture of D7. Generalised osteoporosis.
C. Fracture of right femoral neck with bone absorption on both sides.
From Murray: Brit J. Radiol. **33**: 1–19, 1960.

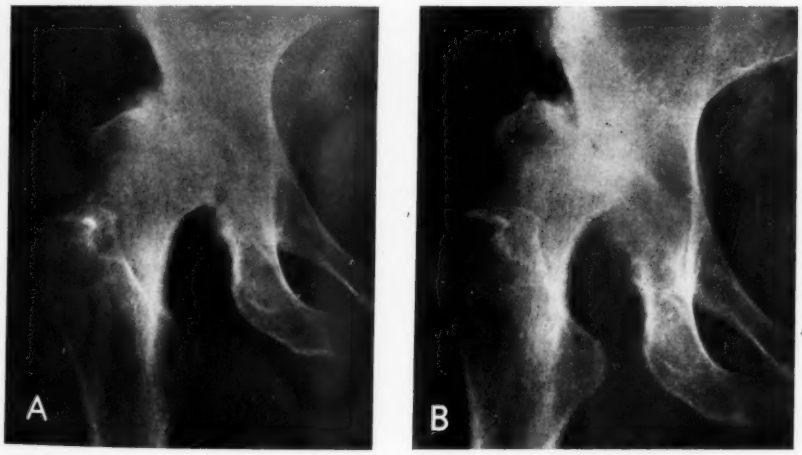

Fig. 4. Case IV: Roentgenograms following oral steroid treatment for fifteen weeks. In addition to the severe destruction and subluxation of the right hip there was noticeable progression of the arthritic changes in the left hip, which was painless. A. May 1959. B. October 1959.
From Sweetnam, Mason, and Murray: Brit. M. J. **1**: 1392–1394, 1960.

become complete through such movement as could have taken place while the patient was being nursed in bed.

CASE IV: (By courtesy of Mr. C. M. Murray). In February 1959, a 51-year-old man who had complained of discomfort in his knees for a few

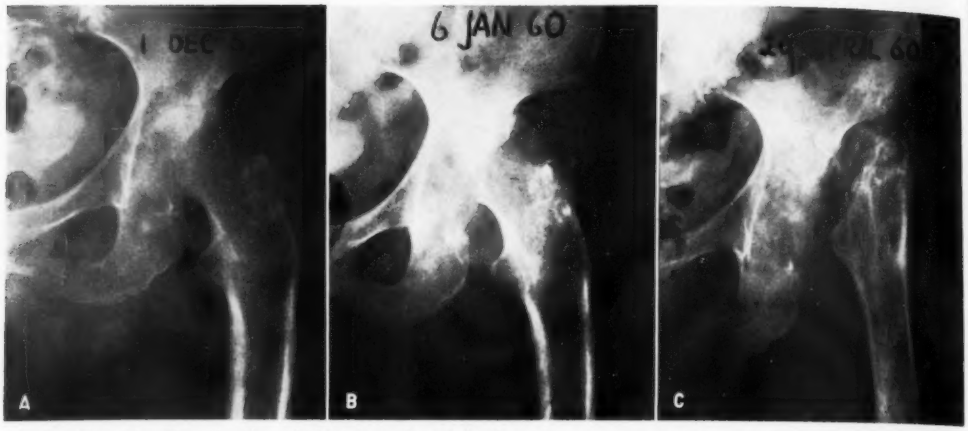

Fig. 5. Case V: Reactivation of old tuberculous infection of greater trochanter. A. Dec. 1, 1959. B. Jan. 6, 1960. C. April 29, 1960.

months, was given butazolidine and prednisodone (10 mg. per day). He remained well until May 1959, when his right hip, suddenly and without pain, "locked" and he was temporarily unable to move it. A radiograph (Fig. 4, A) showed a degenerative arthritis in this joint with partial subluxation and a separate fragment of bone lying lateral to the acetabular margin. This was attributed to a painless fracture. The knees, both clinically and radiologically were normal. Steroid therapy was stopped in June 1959, and thereafter pain in the right hip developed with increasing severity. In October 1959, a further radiograph (Fig. 4, B) showed the destructive changes to have become much more severe, the appearance being regarded as a "steroid arthropathy." At the same time minor osteoarthritic changes in the left hip showed evidence of progression.

Pain was relieved and fair function was restored by simple excision of the right femoral head and neck.

CASE V: *Iatrogenic Reactivation of Infection; Tuberculosis of Hip* (By courtesy of Mr. E. S. Evans). From January to April 1959, a 78-year-old woman was given 75 mg. of cortisone daily. She had complained of pain in her knees for five years, and this therapy afforded complete relief. In July 1959, pain developed in the left hip, in which region any previous symptoms were denied. Further steroids were given without significant relief. Though initially not greatly handicapped, by the end of October the patient was confined to bed.

The radiograph of Dec. 1, 1959 (Fig. 5, A), showed extensive destruction of the left greater trochanter with surrounding calcified debris, which appeared to have resulted from an old, and presumably asymptomatic, tuberculous infection. Such an appearance, if the joint had escaped involvement, is not unduly remarkable in a patient of this age. The film, however, also showed narrowing of the joint space and ill-defined erosions on the lateral aspects of the femoral head and acetabulum. These changes were taken to indicate active tuberculous joint infection, and steroid therapy was discontinued.

On Jan. 6, 1960 (Fig. 5, B), destruction of the upper portion of the femoral head and much of the acetabulum, with the formation of a lateral abscess, which had displaced the old calcified lesions, was demonstrated. Synovial biopsy and abscess drainage, without removal of bone, greatly relieved the pain and gave pathological confirmation of the diagnosis.

On April 29, 1960 (Fig. 5, C), the patient was free of pain and had made excellent clinical progress, but the radiograph of this date showed even more severe destruction of the femoral head and neck.

The destructive changes in this proved tuberculous infection progressed unusually rapidly, and the lesion was considered to have originated from reactivation of the old trochanteric infection during steroid therapy.

INTRA-ARTICULAR STEROID THERAPY

Local treatment of arthritic joints by intra-articular injection of steroids has been widely adopted and has been generally regarded as beneficial. Both Hollander (1953) and Kendall (1958) reported series of many thousands of such injections which were virtually without adverse reactions. Chandler and Wright (1958), however, investigated the effects of intra-articular therapy for rheumatoid arthritis on 25 knees in 18 patients and came to some different conclusions. In 13 of these joints deterioration was observed radiologi-

cally. Nevertheless, the majority showed clinical improvement as judged by the criteria of pain, walking time, and range of movement. Such treatment was considered to be potentially dangerous. It was pointed out that the clinical success achieved by the relief of pain in such joints permits them to be subjected to stresses and strains which would not normally be tolerated, so that bony structures which have already suffered pathological change become subject to accelerated destruction.

CASE VI: (By courtesy of Dr. R. M. Mason). A 57-year-old female had first suffered from rheumatoid arthritis at the age of twenty-five. In 1957 discomfort in the left hip gave place to definite pain on weight-bearing and produced considerable interference with function. In July 1958, hydrocortisone, 100 mg., was injected into the hip. No relief followed and a further injection of 125 mg. was given. Again there was no improvement and, in spite of a third injection in September 1958, of 30 mg. of prednisolone trimethyl acetate, the pain remained unchanged. It did not increase, but during the following six months the hip became unstable and this proved to be as great an impediment to walking as the pain.

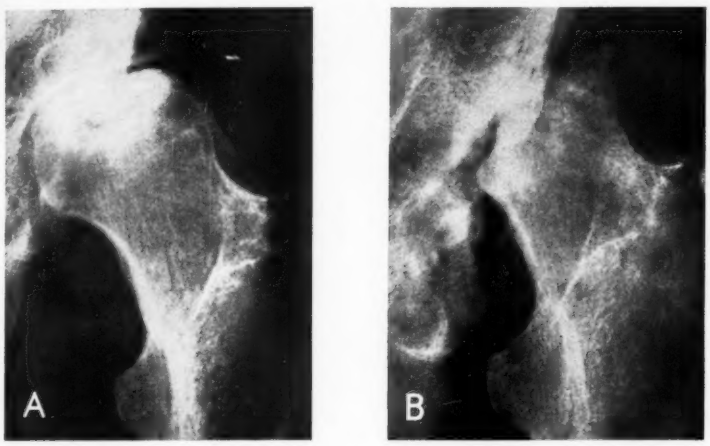

Fig. 6. Case VI: Severe rheumatoid arthritis treated by three intra-articular steroid injections into the hip. No other steroid therapy had been given at any time. A. July 1958. B. April 1959.
From Sweetnam, Mason, and Murray: Brit. M. J. 1: 1392–1394, 1960.

Chandler, Jones, Wright, and Hartfall (1959) reported the remarkable effect of steroid injections into an osteoarthritic hip in a female patient aged fifty-six. Pain was completely relieved but, after eighteen months, mechanical disability developed and it was found that degenerative changes comparable to a true neuropathy had taken place.

In the same way asymptomatic joint infections have been observed (Ansell, 1958; Murray, 1960), but the majority of authors (Rabinowitz, 1955; Thomet, 1957; Tondreau, Hodes, and Schmidt, 1959) have found septic arthritis in these patients to be accompanied by more or less severe pain. The explanation for this variation in response is obscure.

The degenerative changes shown in July 1958 (Fig. 6, A) were of the type seen in old rheumatoid arthritis with secondary osteoarthritis. In April 1959 (Fig. 6, B), however, gross degenerative changes having the appearance of a neuropathy had developed, with much destruction of the femoral head and of a large portion of the acetabulum.

These degenerative changes are comparable to those resulting from oral steroid therapy. The pain was not relieved significantly but was considered to be less severe than might have been expected from the gross degenerative changes which were demonstrated.

CASE VII: *Iatrogenic Spread of Infection; Pyogenic Arthritis of Shoulder* (By courtesy of Dr. A. C. Glendinning). A 73-year-old man was seen on April 16, 1958, with pain in the right shoulder Radiographs revealed extensive para-articular erosions of the head of the right humerus, with some haziness of the articular surface and a few flakes of

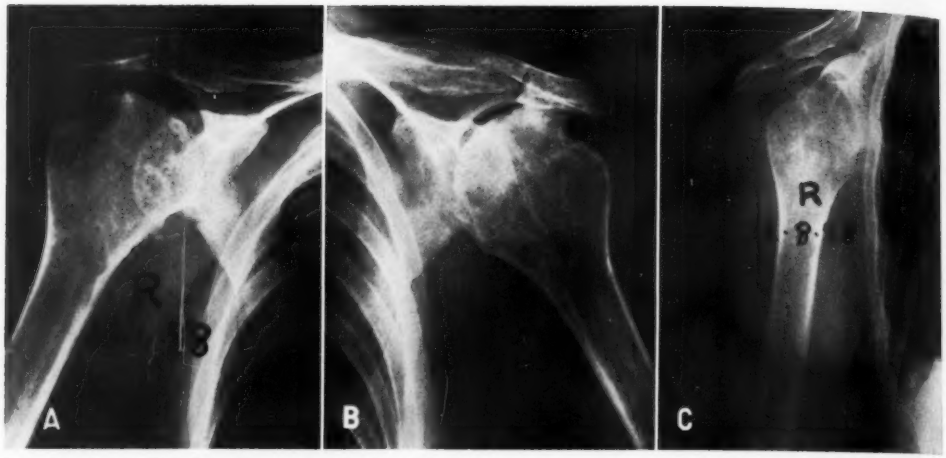

Fig. 7. Case VII: Iatrogenic spread of infection; pyogenic arthritis of shoulder; intra-articular therapy.
A. Para-articular and articular erosion of head of humerus.
B. Typical changes of rheumatoid arthritis in left shoulder.
C. Severe articular erosion of articular surfaces of humeral head and glenoid fossa. Large associated abscess, which was almost asymptomatic.
From Murray: Brit. J. Radiol. **33**: 1–19, 1960.

calcification in the adjacent soft tissues (Fig. 7, A). The provisional diagnosis of rheumatoid arthritis was supported by examination of the left shoulder (Fig. 7, B), where similar para-articular erosions of the humeral head were demonstrated. In retrospect, however, the poor definition of the articular surface of the right humeral head was consistent with the presence of early infection.

Three intra-articular injections of hydrocortisone were given into the painful right shoulder. The patient did not attend further until four months later, when he complained primarily of a large swelling in the right shoulder region. During the previous two months this had been slowly increasing in size and was considered, on clinical examination, to be an abscess. A radiograph of Aug. 22, 1959 (Fig. 7, C) revealed extensive erosion of the articular surfaces of both the humeral head and of the scapula, with a very large associated soft-tissue swelling. This appearance was typical of an active infective arthritis. The generalised osteoporosis, the articular erosion without reactive sclerosis, and the large and relatively asymptomatic abscess together suggested that this infection might well have been tuberculous. After drainage of the abscess, however, the organism was found to be pyogenic. The patient died of pyaemia in January 1959.

This case illustrates alarming, and eventually fatal, progress of infection, with marked suppression of symptoms, following intra-articular use of relatively small quantities of steroids.

DISCUSSION

Radiology has been described as a blunt weapon in the diagnosis of metabolic disease. Nevertheless, it may offer the first evidence of side-effects in Cushing's syndrome and steroid therapy which have not previously been suspected owing to the suppression of symptoms. It should be emphasised that these side-effects are not common and their existence should not be regarded as a contraindication to the use of this therapy. It is already generally appreciated that prolonged use of these hormones is likely to produce some of these complications, but experience has also shown that such undesirable side-effects may present in relatively short periods after comparatively small dosage. When such treatment is undertaken, therefore, the clinician should constantly have in mind the dangers which may supervene.

Mechanical degeneration of joints, akin to neuropathies, is a feature of relatively recent recognition. Such changes may occur either with general or local therapy, and in each instance the earlier stages of degeneration are almost certainly due to avascular necrosis occurring in the presence of unfelt trauma. These changes have not been observed in Cushing's syndrome of natural origin.

Infections of bones and joints which remain unrecognized owing to their failure

to provoke significant symptoms probably represent the most disturbing complication. But, whereas, they are particularly liable to remain undiagnosed with oral therapy, joints becoming infected after intra-articular injections more commonly do become painful. Once such infections have been diagnosed, all the armament of antibiotics is available. It is possible that some instances of painless and fulminating joint infections have not been recorded in the literature through an understandable lack of desire to publicise such unfortunate sequelae.

The variation that takes place in the degree and duration of such symptoms cannot easily be explained. Whereas it may be accepted that painful stimuli are suppressed during the administration of steroids, it is difficult to understand why, in some cases, analgesia should be prolonged after cessation of therapy. This is seen in such cases as are exemplified by Case V. Yet in others, as in Case IV, withdrawal heralds the return of the pain which would normally be expected with such severely destructive lesions. The variation in the quantity of steroids which will suppress symptoms is another aspect of this problem for which no satisfactory answer can be provided. It is quite remarkable that the abnormalities discussed should show such a wide range, both in time of onset and in the period and quantity of treatment necessary for their production.

SUMMARY

Cushing's syndrome of obesity, hypertension, weakness, and depression of sexual function, is associated with overproduction of the adrenocortical steroids, particularly cortisone and hydrocortisone. These excess steroids are produced as a result of hyperplasia or neoplasia of the adrenal cortex. The literature of the radiological changes encountered in the skeleton in this condition is reviewed. The main radiological changes include:

1. *Osteoporosis* of a widespread nature, which is more easily demonstrated in the axial than in the appendicular skeleton.

2. *Pathological fractures*, which may occur anywhere in the weakened skeletal structures but are most commonly seen in the spine, ribs, and pelvis.

3. *Pseudo-callus formation*, having a "cotton-wool" appearance. This develops round the fractures and, in particular, appears to be responsible for the sign of marginal condensation, described in connection with crush fractures of vertebral bodies. This calcification represents an incomplete attempt at fracture healing, associated with inhibition of osteoblastic function by the excess hormones.

4. *Delay in skeletal development.*

Attention is drawn to the clinical facts that (*a*) pain is often completely suppressed in association with these fractures and (*b*) a fatal outcome of the disease is commonly due to infection.

Iatrogenic disease of the skeleton resulting from adrenocortical steroid therapy: Steroids were introduced for therapeutic use in 1948 and first reports of their causation of iatrogenic disease appeared in 1950. The following iatrogenic complications are considered.

1. *Cushing's syndrome*, which cannot be differentiated radiologically from the natural form of the disease, has been frequently described. It is liable to occur with a cortisone or cortisone-equivalent dosage of 50 to 100 mg. a day over periods varying from six months to three years.

2. *Osteoporosis, fractures, and joint degenerations* may be observed in the absence of the fully developed picture of Cushing's syndrome. Such changes may occur after much shorter periods of steroid therapy. These fractures exhibit the same pseudo-callus formation as that seen in connection with Cushing's syndrome. Associated pain tends to be suppressed, or even completely absent, except in the case of vertebral compression fractures, where girdle pains are common, due possibly to secondary nerve-root irritation. Joint degenerations, in some cases approximating a Charcot neuropathy in appearance, are not uncommon, particularly in the hips

and knees, and have been observed as a result of both oral therapy and local intra-articular injections. They are attributed to the improved sense of well-being engendered, with consequent increase of mobility and subjection to greater trauma in the absence of the warning sense of pain. For some reason, so far unexplained, pain may continue to be suppressed, even after withdrawal of therapy.

3. *Bone and joint infections* may develop more easily and spread more rapidly and more silently in the absence of the normal sense of pain and with the suppression of the normal reaction of the body to inflammation. Intra-articular therapy carries with it another hazard. The introduction of infection is dangerous, since symptoms are sometimes suppressed. This appears to be less common than with oral therapy, but a florid, though painless, infective arthritis may lead to a fatal termination.

4. *Delay in skeletal development* may also occur in children.

It is pointed out that such complications are not frequent and that they are not in themselves an indication for the cessation of steroid therapy, since many of these effects can be overcome by the employment of other protective hormones and antibiotic drugs.

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REFERENCES

ALBRIGHT, F., PARSON, W., AND BLOOMBERG, E.: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis; Results of Treatment With Testosterone Propionate. J. Clin. Endocrinol. **1**: 375–384, May 1941.

Annotation. Osteoporosis and Cortisone. Brit. M. J. **1**: 278, Jan. 29, 1955.

ANSELL, G.: Complications of Adrenocortical Therapy. A Radiological Survey. J. Fac. Radiologists **9**: 113–126, July 1958.

BADLEY, B. W., AND ANSELL, B. M.: Fractures in Still's Disease. Ann. Rheumat. Dis. **19**: 135–142, June 1960.

BAER, G. J.: Fractures in Chronic Arthritis. Ann. Rheumat. Dis. **2**: 269–272, December 1941.

BLODGETT, F. M., ET AL.: Effects of Prolonged Cortisone Therapy on Statural Growth, Skeletal Maturation and Metabolic Status of Children. New England J. Med. **254**: 636–641, April 5, 1956.

BOLAND, E. W.: Prolonged Uninterrupted Cortisone Therapy in Rheumatoid Arthritis. Brit. M. J. 2: 191–198, July 28, 1951.

BOLAND, E. W., AND HEADLEY, N. E.: Management of Rheumatoid Arthritis With Smaller (Maintenance) Doses of Cortisone Acetate. J.A.M.A. **144**: 365–372, Sept. 30, 1950.

CHANDLER, G. N., JONES, D. T., WRIGHT, V., AND HARTFALL, S. J.: Charcot's Arthropathy Following Intra-Articular Hydrocortisone. Brit. M. J. **1**: 952–953, April 11, 1959.

CHANDLER, G. N., AND WRIGHT, V.: Deleterious Effect of Intra-Articular Hydrocortisone. Lancet 2: 661–663, Sept. 27, 1958.

CHARCOT, J. M.: Arch. physiol. norm. et path. 1: 161, 1868.

CURTISS, P. H., JR., CLARK, W. S., AND HERNDON, C. H.: Vertebral Fractures Resulting from Prolonged Cortisone and Corticotropin Therapy. J.A.M.A. **156**: 467–469, Oct. 2, 1954.

CUSHING, H.: Basophil Adenomas of Pituitary Body and Their Clinical Manifestations. Bull. Johns Hopkins Hosp. **50**: 137–195, March 1932.

DEMARTINI, F., GROKOEST, A. W., AND RAGAN, C.: Pathological Fractures in Patients with Rheumatoid Arthritis Treated with Cortisone. J.A.M.A. **149**: 750–752, June 21, 1952.

DENT, C. E.: Idiopathic Osteoporosis. Proc. Roy. Soc. Med. **48**: 574–578, July 1955.

DUTHIE, R. B., AND BARKER, A. N.: Histochemistry of Preosseous Stage of Bone Repair Studied by Autoradiography; Effect of Cortisone. J. Bone & Joint Surg. **37-B**: 691-710, November 1955.

EISENHARDT, L., AND THOMPSON, K. W.: Brief Consideration of Present Status of So-Called Pituitary Basophilism, with a Tabulation of Verified Cases. Yale J. Biol. & Med. **11**: 507–522, May 1939.

EISENSTADT, W. S., AND COHEN, E. B.: Osteoporosis and Compression Fractures from Prolonged Cortisone and Corticotropin Therapy. Ann. Allergy **13**: 252–256, May-June 1955.

ELOESSER, L.: Nature of Neuropathic Affections of Joints. Ann. Surg. **66**: 201–207, August 1917.

FOLLIS, R. H., JR.: Pathology of Osseous Changes in Cushing's Syndrome in Infants and in Adults. Bull. Johns Hopkins Hosp. **88**: 440–455, May 1951.

FREYBERG, R. H., AND GRANT, R. L.: Calcium and Phosphorus Metabolism in Verified Case of Pituitary Basophilism. Arch. Int. Med. **58**: 213–228, August 1936.

GRAHAM, W.: Discussion of paper "The Effect of Steroid Hormones on the Growth of Connective Tissue," by C. M. Plotz, J. W. Blunt, R. Lattes, and C. Ragan. Ann. Rheumat. Dis. **9**: 400, December 1950.

HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H., AND POLLEY, H. F.: Effect of Hormone of Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone; Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis; Preliminary Report. Ann. Rheumat. Dis. **8**: 97–104, June 1949.

HOLLANDER, J. L.: Intra-articular Hydrocortisone in Treatment of Arthritis. Ann. Int. Med. **39**: 735–746, October 1953.

HOWLAND, W. J., JR., PUGH, D. G., AND SPRAGUE, R. G.: Roentgenologic Changes of the Skeletal System

in Cushing's Syndrome. Radiology **71:** 69–78, July 1958.

KENDALL, P. H.: Untoward Effects Following Local Hydrocortisone Injection. Ann. Phys. Med. **4:** 170–175, February 1958.

LUDER, J.: Vertebral Collapse After Cortisone Therapy. Great Ormond St. J. June 1954, pp. 15–21.

MARGOLIS, H. M., AND CAPLAN, P. S.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) in Rheumatoid Arthritis. J.A.M.A. **145:** 382–389, Feb. 10, 1951.

MILLS, L. C., BOYLSTON, B. F., GREENE, J. A., AND MOYER, J. H.: Septic Arthritis as a Complication of Orally Given Steroid Therapy. J.A.M.A. **164:** 1310–1314, July 20, 1957.

MURRAY, R. O.: Radiological Bone Changes in Cushing's Syndrome and Steroid Therapy. Brit. J. Radiol. **33:** 1–19, January 1960.

PIETROGRANDE, V., AND MASTROMARINO, R.: Ortop. e traumatol. **25:** 971, 1957.

RABINOWITZ, M. S.: Pyarthrosis of Knee Joint Following Intraarticular Hydrocortisone. Bull. Hosp. Joint. Dis. **16:** 158–170, October 1955.

DE SÈZE, S., HUBAULT, A., AND RENIER, J. C.: Rev. rhum. **20:** 193, 1953.

SISSONS, H. A.: Osteoporosis of Cushing's Syndrome. J. Bone & Joint Surg. **38-B:** 418–433, February 1956.

SISSONS, H. A., AND HADFIELD, G. J.: Influence of Cortisone on Repair of Experimental Fractures in Rabbit. Brit. J. Surg. **39:** 172–178, September 1951.

SOFFER, L. J., AND BADER, R.: Corticotropin and Cortisone in Acute Disseminated Lupus Erythematosus. J.A.M.A. **149:** 1002–1008, July 12, 1952.

SOSMAN, M. C.: Cushing's Disease—Pituitary Basophilism. Am. J. Roentgenol. **62:** 1–32, July 1949.

SPRAGUE, R. G., ET AL.: Observations on Physiologic Effects of Cortisone and ACTH in Man. Arch. Int. Med. **85:** 199–258, February 1950.

STEINBROCKER, O., ET AL.: ACTH and Cortisone as Therapeutic Agents in Arthritis and Some Locomotor Disorders. Bull. New York Acad. Med. **27:** 560–576, September 1951.

STEINER, R. E.: Personal communication, 1958.

STOREY, E.: The Effect of Continuous Administration of Cortisone and its Withdrawal on Bone. Australian & New Zealand J. Surg. **27:** 19–30, August 1957. The Effect of Intermittent Cortisone Administration in the Rabbit: Induction of Cycles of Resorption and Deposition of Bone. J. Bone & Joint Surg. **40-B:** 103–115, February 1958.

SUSSMAN, M. L., AND COPLEMAN, B.: The Roentgenographic Appearance of the Bones in Cushing's Syndrome. Radiology **39:** 288–292, September 1942.

SWEETNAM, D. R., MASON, R. M., AND MURRAY, R. O.: Steroid Arthropathy of the Hip. Brit. M. J. **1:** 1392–1394, May 7, 1960.

TEICHER, R., AND NELSON, C. T.: Osteoporosis and Pathological Fractures Following Treatment with ACTH and Cortisone. J. Invest. Dermat. **19:** 205–210, September 1952.

THOMET, M.: Le danger des injections intraarticulaires d'hydrocortisone. Praxis **46:** 152–153, February 1957.

TONDREAU, R. L., HODES, P. J., AND SCHMIDT, E. R., JR.: Joint Infections Following Steroid Therapy. Am. J. Roentgenol. **82:** 258–270, August 1959.

WANG, C. C., AND ROBBINS, L. L.: Cushing's Disease: Its Roentgenographic Findings. Radiology **67:** 17–24, July 1956.

ZAOUSSIS, A. L., AND JAMES, J. I.: The Iliac Apophysis and the Evolution of Curves in Scoliosis. J. Bone & Joint Surg. **40-B:** 442–453, August 1958.

SUMMARIO IN INTERLINGUA

Steroides e le Skeleto

Le syndrome de Cushing—de obesitate, hypertension, debilitate, e depression del function sexual—es associate con hyperproduction del steroides adrenocortical, particularmente de cortisona e hydrocortisona. Le major alterationes radiologic include extense grados de osteoporosis, fracturas pathologic, formation de pseudocallo de apparentia "lanose" circum le fracturas, e retardo in le disveloppamento skeletic. Le aspectos clinic del condition include le suppression de dolor que deberea esser associate can le fracturas pathologic e le frequentemente mortal termino causate per infection.

Therapia steroide—usate primarimente pro arthritis rheumatoide—pote producer omne le alterationes in le skeleto que es recognoscite in connexion con le syndrome de Cushing de origine natural. In le presente communication, certe complicationes iatrogenic es considerate in connexion con le presentation de casos illustrative. Iste complicationes es: (1) Syndrome de Cushing, non differentiabile in le radiogramma ab le morbo de occurrentia natural, tendente a manifestar se post cursos de inter sex menses e tres annos de cortisona (o le equivalente de cortisona) in un dosage diurne de 50 a 100 mg per die; (2) osteoporosis, fracturas, e degeneration articular, occurrente post plus curte periodos de therapia a steroides, associate con suppression del expectate dolor; (3) disveloppamento e extension rapide de infection ossee e articular, in le absentia de un normal senso de dolor e del responsa usual del corpore a inflammation; e (4) retardo del disveloppamento skeletic in juveniles.

Le supra-describite complicationes non es frequente, e in se mesme illos non representa un indication pro le suspension del therapia a steroides, proque le majoritate de illos pote esser vincite per medio del uso protectori de altere hormones e drogas antibiotic.

Pelvo-Spondylitis in Rheumatoid Arthritis[1]

WILLIAM MARTEL, M.D., and IVAN F. DUFF, M.D.

ATTENTION HAS recently been focused on the clinical differences between rheumatoid arthritis and ankylosing spondylitis and the justification for considering these as related diseases has been seriously questioned (1, 2). Cervical spondylitis frequently occurs in adults with classical rheumatoid arthritis, and the sacroiliac joints may be affected as well (3, 4). Erosions of the ischial tuberosities (4) and symphysis pubis have also been noted in some of these patients. It seemed pertinent, therefore, to determine whether such lesions are common in rheumatoid arthritis and whether they bear any resemblance to the lesions of ankylosing spondylitis.

ANATOMY

The sacroiliac joints are true diarthroses (5–7). They possess a hyaline articular cartilage (which is two to three times thicker on the sacral than on the iliac surface), a joint cleft, synovial membrane, and fibrous capsule. Normally they have slight motion, but osteoarthritic changes are frequent as early as the fourth decade, and a resultant immobility is therefore common, especially in males; it is for this reason that these joints are sometimes spoken of as amphiarthroses. Such osteoarthritic fusion tends to be superficial and is easily differentiated pathologically from the solid intra-articular bony union of ankylosing spondylitis (7).

Accurate radiologic evaluation of these joints is difficult because of their variable and peculiar morphology (8). Their articular surfaces are crescentic or ear-shaped in outline and often present reciprocal, interlocking depressions and ridges. The sacral surface is slightly convex, while the iliac side is concave. The direction of the articular cleft can vary considerably within the joint but is roughly oblique, from front to back, so that in the anteroposterior view the anterior margin is usually projected lateral to the posterior contour. The extent of the articular surface is shown in Figure 1. Accessory sacroiliac joints have also been described (9).

In a symphysis the two opposed bony surfaces are coated with hyaline cartilage, united with fibrocartilage, and reinforced by ligamentous bands. There is no joint cavity, but a small cleft may be seen. Examples are found in the symphysis pubis, the joints between vertebral bodies, and the sternomanubrial joint (10), although the last named is often regarded as a synchondrosis because replacement of cartilage by bone frequently occurs late in life. It is of interest, in connection with the ischial erosions in rheumatoid arthritis, that an inconstant synovial bursa may be seen adjacent to the ischial tuberosity and the latter serves as an attachment for the sacrotuberous ligament and a number of tendons.

METHOD OF STUDY

Frontal and lateral roentgenograms of the spine and frontal films of the pelvis were obtained from patients with rheumatoid arthritis and ankylosing spondylitis. These were selected largely because of the severity of their disease, though a number came under observation because of painful or limited neck motion. Each disease group consisted of 40 patients. Flexion views of the cervical spine were routinely included and oblique projections of the spine, angled views of the sacroiliac joints, and laminagrams were frequently employed when an abnormality was suspected.

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The clinical records of both groups of patients were consulted in regard to limitation of spinal motion or of chest expansion, the presence of rheumatoid nodules, the rheumatoid factor, or visceral involvement, and the occurrence and character of peripheral arthritis. All but 1 of the patients with rheumatoid arthritis and sacroiliac joint involvement were recalled for confirmation and evaluation of any changes in the clinical findings.

Fig. 1. Anatomic specimen. A metallic wire denotes the circumference of the articular surface of the right sacroiliac joint. The iliac and sacral margins superior to the joint (straight arrow) and the tuberosity of the ilium, which is posterior (curved arrow), are the sites of ligamentous attachments and do not form part of the sacroiliac joint proper.

RESULTS

The clinical data in the rheumatoid arthritis group are summarized in Table I. Thirty-nine of the 40 patients had classical rheumatoid arthritis (11) and the diagnosis was definite in the remaining case. Twenty-six of the number were females; 15 were less than forty-five years of age and 32 were less than sixty. In 28 the disease had been present for more than ten years. In all peripheral joint involvement was manifest early in the course. With a single exception (Case III), the onset occurred after the age of sixteen. The disease was considered as Stage III to IV progression (12) in 38 cases and was particularly severe in 30, with progressive destruction of the peripheral joints. Six patients had spontaneous peripheral tendon ruptures. Rheumatoid nodules were seen in 65 per cent, and the rheumatoid factor was positive in 80 per cent. Nineteen patients had systemic or visceral abnormalities frequently associated with rheumatoid arthritis,[2] and 24 had significant hypercortisonism due to intensive or prolonged steroid therapy. Peptic ulcer developed in 8 patients, 5 of whom were receiving steroid therapy.

The clinical findings in the 40 patients with ankylosing spondylitis are also shown in Table I. This group was somewhat younger than that with rheumatoid arthritis, and only 7 were females; the duration of the disease was comparable in the two groups. Six of these patients had periph-

[2] Including any of the following: splenomegaly, anemia, leukopenia, lupus erythematosus cell phenomenon, cardiac-valvular or pericardial lesions, Sjögren's syndrome, scleromalacia, iritis, episcleritis, polyarteritis.

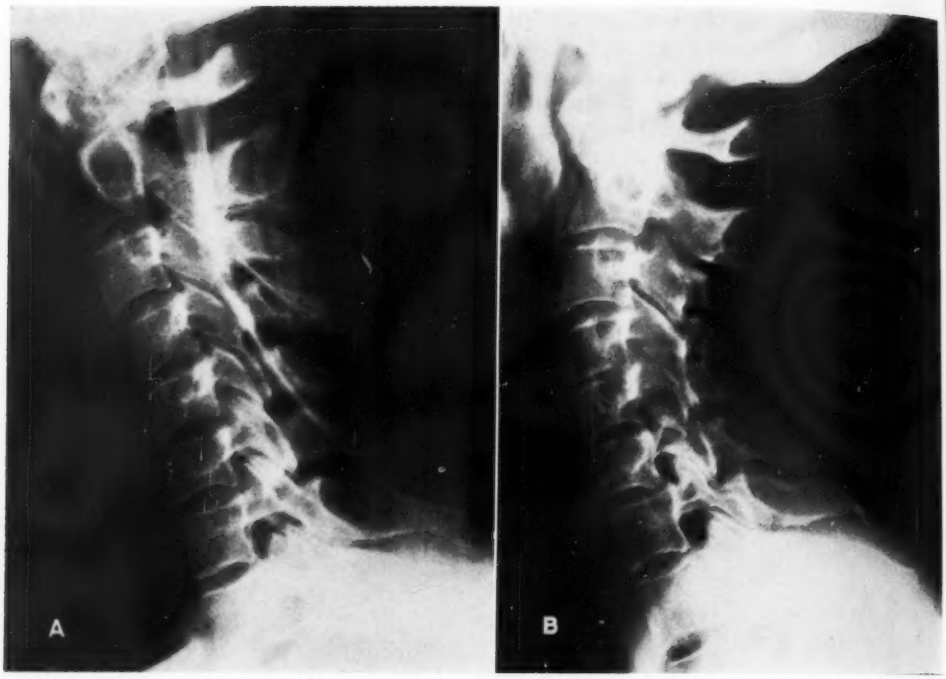

Fig. 2. Case I. A. 1951. B. 1960. The atlanto-axial subluxation has increased and erosions of the spines of C7 and D1 and ankylosis of the apophyseal joints of C4-C5 and C5-C6 have developed. The bodies of C4 and C5 have become reduced in size and the height of the intervening intervertebral disk has diminished.

TABLE I: CLINICAL DATA IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

	Rheumatoid Arthritis	Ankylosing Spondylitis
No. of patients	40	40
Sex ratio		
F	26	7
M	14	33
Age		
Less than 45 years	15	27
Less than 60 years	32	38
Duration		
More than 10 years	28	32
More than 20 years	11	18
Peripheral arthritis*	40	6
Limitation of motion in lower spine	3	33
Reduced chest expansion	3	22
Rheumatoid nodules	26	0
Rheumatoid factor		
Number positive	32	5
Number tested	40	21

* Joints of the hands, wrists, feet, or ankles.

eral arthritis and 14 others had involvement of the hips or shoulders. Motion in the lower spine was significantly limited in the majority, and chest expansion was reduced in approximately 50 per cent. None had rheumatoid nodules: 5 of the 21 patients who were tested for the rheumatoid factor showed a positive result; only 1 of these 5 had peripheral joint involvement. Four of the 40 patients had psoriasis (13), and 2 had chronic ulcerative colitis (14).

Thirteen patients with rheumatoid arthritis had sacroiliac joint involvement (Table II). All of these had classical disease according to the established criteria (11), but the clinical features in 1 (Case VI) justified uncertainty as to whether the condition was rheumatoid

TABLE II: DATA IN 13 PATIENTS WITH RHEUMATOID ARTHRITIS AND SACROILIAC ARTHRITIS

Sex ratio	
F	7
M	6
Age, less than 45 years	6
Duration, more than 10 years	10
Rheumatoid nodules	9
Rheumatoid factor	12
Painful or limited neck motion	12
Sacroiliac joint fusion	4
Cervical subluxation or bone erosion	13
"Squaring" or syndesmophytes	1
Symphysis pubis erosion	3
Ischial tuberosity erosion	5

arthritis or ankylosing spondylitis. Seven patients were females, 6 were less than forty-five years of age, and in 10 the duration of the disease was more than ten years. Rheumatoid nodules were seen in 9 patients and all but 1 (Case VI) had the rheumatoid factor. All had either cervical vertebral erosions or subluxations, and almost all had painful or limited neck motion. Ankylosis had occurred in the cervical apophyseal joints in 2 patients (Cases I and V), and in 7 one or more of the cervical intervertebral disks were reduced in height, without adjacent osteophytes. Although some of these patients had slight reduction in chest expansion or limitation of motion in the lower spine, in only 1 (Case VI) were these findings outstanding. "Squaring" and syndesmophytes, similar to the lesions of ankylosing spondylitis, were limited to the cervical spine in 1 patient (Case V). Similar changes were present in the lower dorsal and upper lumbar spine in another (Case II) but were minimal and barely perceptible. In Case II erosions of the bony margins of the symphysis pubis were also exhibited. In 2 instances cyst-like changes were present. Ischial tuberosity erosions were noted in 5 cases. In 3 others the ischial tuberosities showed periosteal new bone formation without erosive changes or reactive sclerosis, but this was minimal and of questionable significance.

Table III is a comparison of the radiologic findings in rheumatoid arthritis and ankylosing spondylitis. In 4 patients with rheumatoid arthritis, the sacroiliac disease was similar to that seen in a late phase of ankylosing spondylitis: in 1 the joint margins were completely effaced by bony

Fig. 3. Case I. Bilateral subchondral erosions of the sacroiliac joints, with little reactive sclerosis, appear to predominate on the iliac margins.

TABLE III: COMPARISON OF RADIOLOGIC ABNORMALITIES OF THE PELVIS AND SPINE IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

	Rheumatoid Arthritis	Ankylosing Spondylitis
No. of patients	40	40
Sacroiliac arthritis	13	40
Symphysis pubis erosion	3	14
Ischial tuberosity erosion	5	19
Cervical spine		
Vertebral subluxation	27	6
Apophyseal joint ankylosis	3	19
Vertebral erosion	18	3
"Squaring," syndesmophytes	1	24
Decreased disk height	12	16
Calcification, annulus fibrosus	1	10
Dorsolumbar spine		
Apophyseal joint ankylosis	0	21
"Squaring," syndesmophytes	1	31
Decreased disk height	2	15

Fig. 4. Case II. Small, sharply demarcated subchondral erosions of both sacroiliac joints.

Fig. 5. Case II. Erosion of the margins of the symphysis pubis without reactive sclerosis.

ankylosis (Fig. 10), and in the other 3 the cartilage spaces were obliterated (Fig. 11).

In the "erosive phase," the sacroiliac arthritis of rheumatoid arthritis differed from ankylosing spondylitis in that the erosions usually appeared well marginated and associated with minimal, if any, reactive sclerosis. At times they predominated on the iliac side of the joint (Fig. 3). Erosions of the symphysis pubis and ischial tuberosities were less common in rheumatoid arthritis and, unlike those in ankylosing spondylitis, were unattended by much reactive sclerosis or significant bone proliferation (Fig. 5). None of these patients had decubitus ulcers or chronic urinary infection; though all were severely disabled, only 2 were confined to a wheel chair.

A lack of sclerosis and reactive bone formation also characterized the erosions

of the cervical vertebrae in rheumatoid arthritis. These occurred at the tips of the lower cervical spinous processes in 17 patients and in the vertebral end-plates (Fig. 14) in 4. Cervical subluxations, most common in the atlanto-axial joints, were more frequent and severe in rheumatoid arthritis and were multiple in 10 cases. None of the patients with ankylosing spondylitis had multiple subluxations, and apophyseal joint ankylosis was much more common in this group. Three rheumatoid arthritis patients had demonstrable apophyseal joint erosions and in at least 2 these joints were significantly narrowed. Reduced height of the cervical intervertebral disks, without adjacent osteophytes, was frequent in both groups and often multiple. Calcification of the annulus fibrosus was present in only 1 patient with rheumatoid arthritis (Case V), but in 10 of those with ankylosing spondylitis. In 4 patients with ankylosing spondylitis radiologic abnormalities were limited to the sacroiliac joints.

CASE REPORTS

CASE I: E. G., a 47-year-old Negro woman, had classical rheumatoid arthritis for twenty-nine years, with progressive involvement of most of the peripheral joints. She had low back discomfort, but this was not a prominent complaint. Left frontal and occipital headaches, especially on arising in the mornings, and occasional blurring of vision were noted. Rheumatoid nodules were never described. Adrenocortical steroid therapy was administered for approximately one year in 1950. The latex fixation test for the rheumatoid factor was strongly positive (1:5,120). Physical examination showed limitation of motion of the neck but not of the back, and there was no significant reduction in chest expansion. Neurologic examination was negative.

Roentgen films showed advanced rheumatoid arthritis of virtually all the peripheral joints, with destruction of articular cartilage and subchondral bone. There was bony ankylosis of the right elbow and ankle. An atlanto-axial subluxation developed, as well as erosions of the spinous processes of C7 and D1 and ankylosis of the apophyseal joints between C4 and C5, and C5 and C6. The bodies of C4 and C5 became reduced in size, and the height of the intervening intervertebral disk was diminished (Fig. 2). The sacroiliac joints were eroded, without significant subchondral sclerosis (Fig. 3). There was no "squaring" of the vertebral bodies or paraspinal ossifications.

CASE II: I. M., a 32-year-old female with rheumatoid arthritis developing in 1954, noted at that time a tender subcutaneous nodule over the right wrist. She had been unable to stand or care for herself for the past year because of weakness and severe involvement of the peripheral joints. Adrenocortical steroid therapy had been administered in high dosage for at least four years. Slight stiffness of the neck and back had recently developed. Physical examination showed advanced deformities of the peripheral joints and severe muscle wasting, dryness of the mouth, and keratitis sicca (Sjögren's syndrome). Neck motion was reduced and painful but there was no significant limitation of motion in the lower spine or reduction in chest expansion. Neurologic examination was negative. The latex fixation test for the rheumatoid factor was positive (1:5,120).

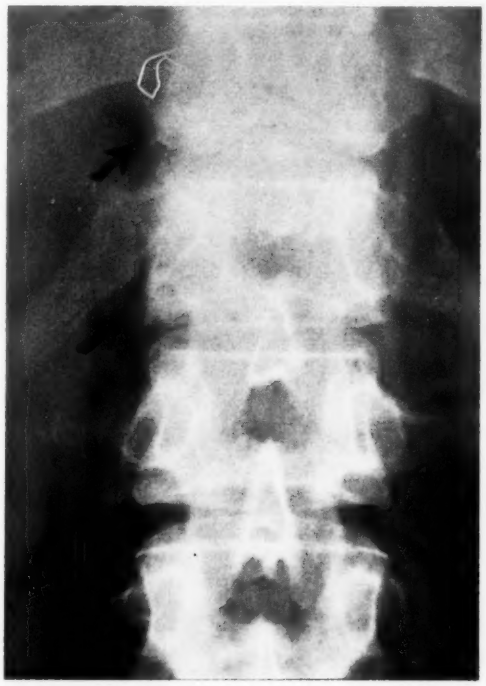

Fig. 6. Case II. Syndesmophytes (arrows) at the margins of D11 and D12 are small and barely perceptible.

Radiographs showed severe involvement of hands, wrists, feet, ankles, knees, and hips, with destruction of cartilage and subchondral bone and multiple subluxations. There were an anterior subluxation of the atlas in flexion (atlanto-odontoid interval, 5 mm.) and slight malalignment between C2, C3, and C4. Small, sharply demarcated subchondral erosions of the sacroiliac joints and symphysis pubis, without reactive sclerosis, were present (Figs. 4 and 5). Syndesmophytes were observed at D10-

D11, and D11-D12 but were small and barely perceptible (Fig. 6). There was questionable "squaring" of D12 and L1 but no sclerosis in the anterior corners of these vertebrae.

CASE III: J. J., a 27-year-old woman, had rheumatoid arthritis for approximately twelve years, resulting in severe peripheral joint deformities and disability. She had slight neck discomfort but no significant symptoms referable to the back. Physical examination showed slight limitation of motion in the neck but not in the dorsolumbar spine, and chest expansion was normal. Subcutaneous rheumatoid nodules were present, and a serologic test for the rheumatoid factor was positive.

megaly, lymphadenopathy, scleromalacia, and multiple, subcutaneous rheumatoid nodules. Polyneuritis and polyarteritis were present. The patient had received adrenocortical steroid therapy but not during the past eight years. Physical examination showed neck motion to be painful and moderately limited, but no significant limitation of motion in the dorsolumbar spine or reduction in chest expansion. Repeated serologic tests for the rheumatoid factor were strongly positive.

Radiologic examination of the extremities disclosed widespread destruction of articular cartilage and resorption of periarticular bone. Cervical spine films demonstrated multiple subluxations, reduced height of the intervertebral disks, and erosions of the

Fig. 7. Case III. Minimal, marginal irregularities of the subchondral bone in the inferior portions of both sacroiliac joints, with reduction in the cartilage spaces. Note the asymmetry of the joints and the variation in the direction of the joint cleft on the right.

Roentgen examination disclosed advanced destruction of the articular cartilage and subchondral bone in the small joints of the hands, wrists, elbows, shoulders, ankles, knees, and left hip. An atlantoodontoid separation of 5 mm. in flexion and erosions of the tips of the spines of C6 and C7 were noted. There were erosions of the subchondral bone in the inferior portions of both sacroiliac joints, with reduction in the cartilage spaces (Fig. 7). "Squaring" of the vertebral bodies and paraspinal ossifications were absent.

CASE IV: C. S.,[3] a 42-year-old female, had mutilating rheumatoid arthritis of virtually all the peripheral joints, which began at the age of twenty-four. This was accompanied by anemia, splenovertebral end-plates, posterior arches, articular processes, and dens. The sacroiliac joint spaces were obliterated, and sharply demarcated erosions of the ischial margins were seen, without adjacent sclerosis (Fig. 8). There were small cyst-like changes at the margins of the symphysis pubis. "Squaring" and syndesmophytes of the dorsolumbar spine were absent. There was bone resorption of the tips of the transverse processes, posterior ends of the ribs, ends of the clavicles, and at the sternomanubrial joint.

CASE V: A. F., a 52-year-old man, had rheumatoid arthritis which began at the age of twenty-one and affected most of the peripheral joints. Severe contracture deformities developed, together with subluxations and numerous subcutaneous rheuma-

[3] Previously reported (19).

toid nodules. Steroid therapy had been given in moderate doses in the past, but not in the last two years. In 1958, splenomegaly and pancytopenia occurred and were successfully treated by splenectomy. Back pain was not a prominent symptom. On physical examination, there was complete absence of neck motion but no significant limitation of motion in the dorsolumbar spine or reduction in chest expansion. Serologic tests for the rheumatoid factor were repeatedly and strongly positive.

Fig. 8. Case IV. Obliteration of the cartilage spaces of both sacroiliac joints; erosions of the ischial tuberosities and small cyst-like changes at the symphysis pubis.

Radiologic examination disclosed extensive destruction of cartilage and subchondral bone in many peripheral joints. Cervical spine films showed "squaring" and syndesmophytes with ankylosis of the apophyseal joints (Fig. 9). There was bone resorption at the tip of the spine of C7. The dorsolumbar spine was normal, but the sacroiliac joints were completely ankylosed, with effacement of the joint margins (Fig. 10).

CASE VI: S. S.[4], a 37-year-old man, had rheumatoid arthritis, developing in the elbows in 1943 and progressing to involve almost all the peripheral joints within a few years. He had been confined to a wheel chair since 1958 (two years) because of deformities of these joints and progressive muscular weakness and fatigue. Low back ache had never been a problem, but he did complain of pain in the neck and over the occiput. There had been episodes of fever, weight loss, and anemia in the past, and uveitis of the right eye developed in 1953. Subcutaneous nodules had never been described. Continuous steroid therapy was administered for five years.

[4] From the VA Hospital, Ann Arbor, Mich.

Fig. 9. Case V. Most of the apophyseal joints are ankylosed and small syndesmophytes bridge the vertebral bodies anteriorly. Some of the latter have a "squared" appearance, and the spine of C7 is "pointed." Note the reduced height of the intervertebral disks and calcification of the annulus fibrosus in some of them.

Physical examination disclosed severe deformities of the peripheral joints with multiple flexion contractures and subluxations and evidence of active synovitis in the ankles, knees, shoulders, wrists, and metacarpophalangeal joints. There was definite limitation of motion in the neck and lower spine, and chest expansion was reduced. A severe microcytic, hypochromic anemia (hemoglobin 8.6 gm. per 100 c.c.) was present. Serologic tests (latex and bentonite) for the rheumatoid factor were negative.

Radiologic examination showed typical findings of rheumatoid arthritis of the peripheral joints with destruction of cartilage and subchondral bone and multiple subluxations and contracture deformities. The cartilage spaces of both sacroiliac joints were obliterated (Fig. 11), and there were erosions of both ischial tuberosities. The apophyseal joints were not ankylosed nor were paraspinal ossifications or "squaring" of the vertebral bodies demonstrated. There was minimal vertebral malalignment of C4-C5 and C5-C6 in flexion.

CASE VII: G. M.,[5] a 54-year-old male, had had rheumatoid arthritis since 1942. Paresthesias and progressive weakness of the upper extremities developed in 1958, together with intermittent episodes of blurred vision and a staggering gait. He had noticed shortening of the neck and crepitus over the cervical spine. Adrenocortical steroids had been taken for eight years. Physical examination showed widespread peripheral arthritis with multiple subcutaneous rheumatoid nodules. There were bilateral extensor digitorum communis tendon ruptures. Neck motion was limited. Muscular weakness of the upper extremities was present, but no sensory impairment. The left biceps, triceps, patellar, and Achilles reflexes were absent. There were no pyramidal tract signs. The latex fixation test was positive (1:5,120).

Fig. 10. Case V. Complete fusion of the sacroiliac joints; the subchondral margins are no longer discerned.

Roentgenograms of the cervical spine showed multiple subluxations, and the atlanto-odontoid interval measured 17 mm. The odontoid process was small and eroded but was in the midline. The atlanto-axial dislocation was reduced and the upper cervical spine was fused. It was noted that the ligamentum flavum between C1 and C2 was absent and the dura filled this space.

Severe pain developed in the upper dorsal spine eighteen months after cervical fusion, and a dorsal kyphoscoliosis and tenderness over D4 and D5 were noted. Roentgen films (Fig. 13) demonstrated erosions of the vertebral end-plates of D3, D4, and D5, with partial vertebral collapse and subluxations. A similar lesion appeared in the cervical spine at C3–C4 (Fig. 14) several months later. Films of the sacroiliac joints and lumbar spine showed normal findings. The *Brucella* agglutination and tuberculin skin tests were negative. Cultures of urine, sputum, and gastric washings were negative for acid-fast bacilli.

[5] Previously reported (4).

DISCUSSION

Although the clinical and pathologic differences between rheumatoid arthritis and ankylosing spondylitis have been emphasized (1, 2, 15, 16), many believe these are the same disease or are at least related. The term "rheumatoid spondylitis" was adopted largely because the small peripheral joints can be affected in ankylosing spondylitis and histologically these lesions are apparently indistinguishable from those of rheumatoid arthritis (17). The sex and age incidence, the mode of onset and distribution of involved joints, the presence of visceral involvement, rheumatoid nodules, and the rheumatoid factor (18–20), the type of associated cardiac lesion, and the effectiveness of various therapeutic agents are some of the features which usually permit easy clinical differentiation of these diseases.

The lack of histologic verification of the spinal and pelvic lesions does not permit definite conclusion regarding their pathogenesis and specificity. Similar lesions

Fig. 11. Case VI. Obliteration of the cartilage spaces of both sacroiliac joints.
Fig. 12. Ankylosing spondylitis. Compare these sacroiliac joints with those in Figs. 8 and 11. The non-articular margins superior to the joints are also fused. Characteristic and extensive lesions of ankylosing spondylitis were present in the dorsolumbar spine.

have been noted radiologically in other conditions (21–25). Gibson (26), however, believes that a specific lesion of the cervical intervertebral disks and adjacent end-plates may occur in rheumatoid arthritis. In this disease involvement of the odontoid process and adjacent ligaments has been reported (27). Rheumatoid nodules have been described in the lumbar vertebrae of a patient who appeared to have rheumatoid arthritis without rheumatoid spondylitis (28, 29).

The sacroiliac arthritis of rheumatoid arthritis (3,4, 30–32) differs from ankylos-

ing spondylitis in that the subchondral erosions are well marginated, without much reactive sclerosis. Obliteration of the cartilage spaces may take place, however, with a variable degree of joint fusion, resulting in an appearance similar to an advanced quiescent phase of ankylosing spondylitis (Fig. 12). This stage is reached late in the disease, at which time advanced changes (33) are generally present in the dorsolumbar spine in ankylosing spondylitis. These changes were not present in any of our 4 rheumatoid arthritis patients with obliteration of the sacroiliac joint spaces. The non-articular, sacroiliac margins, superior to the joints proper (Fig. 1), serve for ligamentous attachments and are frequently affected in ankylosing spondylitis (Fig. 12). It is of interest that in only 1 of our examples of rheumatoid arthritis (Case VI) were these margins involved.

It is possible that the dorsolumbar apophyseal and costovertebral joints are more often affected in rheumatoid arthritis than this study disclosed. Precise evaluation of these joints is difficult and generally requires oblique projections. It is significant, however, that they were frequently found to be fused in ankylosing spondylitis but not in rheumatoid arthritis. Furthermore, resorption of bone, rather than ankylosis, can occur in rheumatoid arthritis at the costovertebral and sternomanubrial joints (Case IV).

Cervical spondylitis often develops in persons with rheumatoid arthritis and normal sacroiliac joints (4, 31, 34, 35; Case VII). Although ankylosis of the apophyseal joints occasionally occurs during adulthood in these patients (Cases I and V), it is far less common than in ankylosing spondylitis and, therefore, cervical subluxations are more prevalent in rheumatoid arthritis. Pain and limitation of neck motion are not unusual, but back

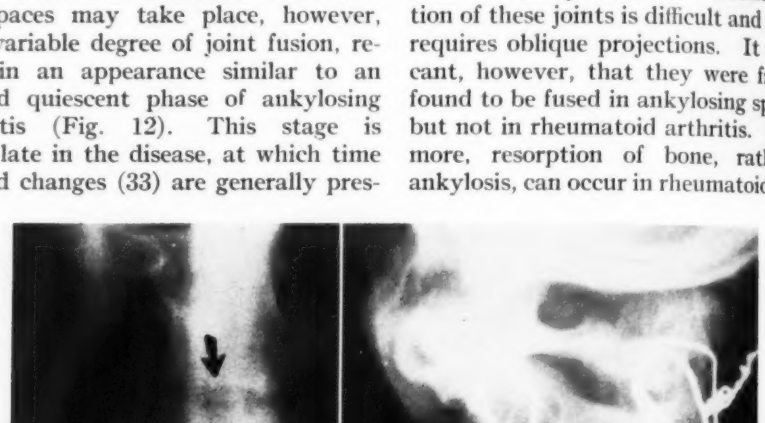

Fig. 13. Case VII. Anteroposterior laminagram, 1959. Erosions of the vertebral end-plates between D3-D4 (arrow) and D4-D5 are shown. Note the subluxations and partial vertebral collapse.

Fig. 14. Case VII. 1960. Erosions of the vertebral end-plates between C3 and C4 (curved arrow) developed approximately two years after spinal fusion for a spontaneous atlanto-axial subluxation. Note the subluxation at C3-C4 and the gaping (arrow) at the laminectomy site posteriorly.

discomfort and reduced chest expansion are uncommon. The sacroiliac and cervical apophyseal joints were ankylosed in Case V but the dorsolumbar spine was normal. Such sparing of the latter has been seen in what apparently was ankylosing spondylitis (36) but it is rare. This pattern of involvement of the cervical spine and sacroiliac joints is frequent, however, in rheumatoid arthritis (3; Table II).

The pelvo-spondylitis in rheumatoid arthritis appears to differ significantly from ankylosing spondylitis. In attempting to distinguish these conditions, it is important to evaluate the clinical manifestations and the radiologic appearance, not only of the sacroiliac joints, but of the entire spine and pelvis. It may be argued that the radiologic differences simply reflect a modified tissue response to a similar basic abnormality and do not necessarily imply that these are different entities. On the other hand, the limited variety of reactions that may take place in connective tissue makes it possible for different diseases to evoke a similar pathologic response and produce the same radiologic appearance. In view of the frequency of pelvo-spondylitis in rheumatoid arthritis, and until we know more about the etiology of these diseases, it seems expedient to bear these apparently significant differences in mind and to define more precisely the term "rheumatoid spondylitis."

SUMMARY

Sacroiliac arthritis may occur in classical rheumatoid arthritis and erosions may be seen in the ischial tuberosities and symphysis pubis. Although the sacroiliac and cervical apophyseal joints may become ankylosed, the spinal lesions of rheumatoid arthritis, for the most part, tend to be nonankylosing and the lack of reactive sclerosis and bone proliferation at the sites of bone erosion is significant. Furthermore, the symptoms of spondylitis and the pattern of involvement, with predilection for the cervical spine, often in patients with normal sacroiliac joints, differ from the findings in ankylosing spondylitis.

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REFERENCES

1. FORESTIER, J.: Spondylarthrite ankylosante et polyarthrite chronique évolutive. Schweiz. med. Wchnschr. **90:** 880–883, Aug. 13, 1960.

2. GRAHAM, W.: Is Rheumatoid Spondylitis a Separate Entity? Arthritis & Rheum. **3:** 88–90, February 1960.

3. SHARP, J.: Differential Diagnosis of Ankylosing Spondylitis. Brit. M. J. **1:** 975–978, April 27, 1957.

4. MARTEL, W., AND PAGE, J. W.: Cervical Vertebral Erosions and Subluxations in Rheumatoid Arthritis and Ankylosing Spondylitis. Arthritis & Rheum. **3:** 546–556, December 1960.

5. SASHIN, D.: Critical Analysis of Anatomy and Pathologic Changes in Sacro-Iliac Joints. J. Bone & Joint Surg. **12:** 891–910, October 1930.

6. BROOKE, R.: The Sacro-Iliac Joint. J. Anat., London **58:** 299–305, 1923.

7. MACDONALD, G. R., AND HUNT, T. E.: Sacro-Iliac Joints. Observations on Gross and Histological Changes in Various Age Groups. Canad. M. A. J. **66:** 157–163, February 1952.

8. SOLONEN, K. A.: The Sacroiliac Joint in the Light of Anatomical, Roentgenological and Clinical Studies. Acta orthop. scandinav. Suppl. 27, 1957, pp. 1–127.

9. HADLEY, L. A.: Accessory Sacroiliac Articulations with Arthritic Changes. Radiology **55:** 403–409, September 1950.

10. GRANT, J. C. B.: A Method of Anatomy: Descriptive and Deductive. Baltimore, Williams & Wilkins Co., 4th ed., 1948, pp. 13–14.

11. ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., AND JESSAR, R. A.: 1958 Revision of Diagnostic Criteria for Rheumatoid Arthritis. Bull. Rheumat. Dis. **9:** 175–176, December 1958.

12. STEINBROCKER, O., TRAEGER, C. H., AND BATTERMAN, R. C.: Therapeutic Criteria in Rheumatoid Arthritis. J.A.M.A. **140:** 659–662, June 25, 1949.

13. FLETCHER, E., AND ROSE, F. C.: Psoriasis Spondylitica. Lancet **1:** 695–696, April 2, 1955.

14. ZVAIFLER, N. J., AND MARTEL, W.: Spondylitis in Chronic Ulcerative Colitis. Arthritis & Rheum. **3:** 76–87, February 1960.

15. CRUICKSHANK, B.: Lesions of Cartilaginous Joints in Ankylosing Spondylitis. J. Path. & Bact. **71:** 73–84, January 1956.

16. CRUICKSHANK, B.: Pathology of Ankylosing Spondylitis. Bull. Rheumat. Dis. **10:** 211–214, March 1960.

17. COLLINS, D. H.: The Pathology of Articular and Spinal Diseases. Baltimore, Williams & Wilkins Co., 1950, p. 321.

18. ZIFF, M.: The Agglutination Reaction in Rheumatoid Arthritis. J. Chron. Dis. **5:** 644–667, June 1957.

19. MCEWEN, C., ZIFF, M., CARMEL, P., DITATA, D., AND TANNER, M.: The Relationship to Rheumatoid Arthritis of its So-called Variants. Arthritis & Rheum. **1:** 481–496, December 1958.

20. MIKKELSEN, W. M., DUFF, I. F., GOODSON, L., COULTER, W. H., AND HERTZ, C.: A Comparative Study of Some Recent Serologic Tests for Rheumatoid Arthritis. Ann. Int. Med. **52:** 1051–1058, May 1960.

21. EYLER, W. R., AND DOUB, H. P.: Extraintestinal Roentgen Manifestations of Intestinal Lipodystrophy. J.A.M.A. **160:** 534–536, Feb. 18, 1956.

22. ABEL, M. S.: Sacroiliac Joint Changes in Traumatic Paraplegics. Radiology **55:** 235–239, August 1950.

23. LODGE, T.: Bone, Joint and Soft Tissue Changes Following Paraplegia. Acta radiol. **46:** 435–445, July-August 1956.

24. MARTEL, W., ABEL, M. R., AND DUFF, I. F.: Cervical Spine Involvement in Lipoid Dermato-Arthritis. Radiology **77:** 613–617, October 1961.

25. WILTSE, L. L., AND FRANTZ, C. H.: Non-Suppurative Osteitis Pubis in the Female. J. Bone & Joint Surg. **38-A:** 500–516, June 1956.

26. GIBSON, H. J.. Ankylosing Spondylitis. Aetiology & Pathology. J. Fac. Radiologists **8:** 193–200, January 1957.

27. MARTEL, W.: Occipito-Atlanto-Axial Joints in Rheumatoid Arthritis and Ankylosing Spondylitis. Am. J. Roentgenol. **86:** 223–240, August 1961.

28. BAGGENSTOSS, A. H., BICKEL, W. H., AND WARD, L. E.: Rheumatoid Granulomatous Nodules as Destructive Lesions of Vertebrae. J. Bone & Joint Surg. **34-A:** 601–609, July 1952.

29. WHOLEY, M. H., PUGH, D. G., AND BICKEL, W. H.: Localized Destructive Lesions in Rheumatoid Spondylitis. Radiology **74:** 54–56, January 1960.

30. DILSEN, A. N., MCEWEN, C., DITATA, D., CARMEL, P., AND GERSH, W. J.: Roentgenologic Features of Ankylosing Spondylitis and Rheumatoid Arthritis. Arthritis & Rheumatism **3:** 441, October 1960.

31. COHEN, A. S., ET AL. The Second Pan American Congress on Rheumatic Diseases and 23rd Annual Meeting of the American Rheumatism Association. Bull. Rheumat. Dis. **10:** 194, September 1959.

32. MASON, R. M., MURRAY, R. S., OATES, J. K., AND YOUNG, A. C.. A Comparative Radiological Study of Reiter's Disease, Rheumatoid Arthritis and Ankylosing Spondylitis. J. Bone & Joint Surg. **41-B:** 137–148, February 1959.

33. ROMANUS, R., AND YDÉN, S.: Pelvo-Spondylitis Ossificans. Copenhagen, Munksgaard, 1955.

34. SHARP, J., PURSER, D. W., AND LAWRENCE, J. S.: Rheumatoid Arthritis of the Cervical Spine in the Adult. Ann. Rheumat. Dis. **17:** 303–313, September 1958.

35. GRAHAM, D. C.: Personal communication.

36. THOMPSON, M., NEWTON, D. R., AND GRAINGER, R. G.: Discussion of the Clinical and Radiological Aspects of Sacro-Iliac Disease. Proc. Roy. Soc. Med., London **50:** 847–858, October 1957.

SUMMARIO IN INTERLINGUA

Pelvo-Spondylitis in Arthritis Rheumatoide

Quaranta patientes con classic arthritis rheumatoide e 40 con spondylitis ankylosante esseva studiate con le objectivo de determinar si spondylitis cervical e erosiones del tuberositates ischial e del symphyse pubic es commun in arthritis rheumatoide e si illos exhibi ulle similitude con le lesiones de spondylitis ankylosante. Roentgenogrammas frontal e lateral del spina dorsal e frontales del pelve esseva obtenite. Expositiones flexional del spina cervical esseva includite routinarimente, e projectiones oblique del spina dorsal, angulates del articulationes sacroiliac, e laminogrammas esseva usate frequentemente in casos in que le presentia de un anormalitate esseva suspicite.

Arthritis sacroiliac pote occurrer in classic arthritis rheumatoide, e erosiones es incontrate in le tuberositates ischial e le symphyse pubic. Ben que le sacroiliac e cervical articulationes apophysee es a vices ankylosate, le lesiones spinal de arthritis rheumatoide—a generalmente parlar—tende a esser non-ankylosante, e le absentia de sclerosis reactive e de proliferation ossee al sitos del erosion ossee es significative. In plus, le symptomas de spondylitis e le configuration general del affectiones (con su predilection pro le spina cervical) que es frequente in patientes sin ulle anormalitate in le articulationes sacroiliac differe ab le constatationes in spondylitis ankylosante.

A Comparative Study of Intraosseous Cavography and Intravenous Pyelography in the Demonstration of Retroperitoneal Lymphoma[1]

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THE RETROPERITONEAL space is subject to a variety of tumors. These may originate from retroperitoneal organs or glands, as the kidney, pancreas, and adrenals, or they may arise primarily in retroperitoneal connective, adipose, nervous, muscular, or even embryonic tissue. The lymphatics may be involved by either primary lymphomas or metastatic lesions, the latter being the most common of the retroperitoneal tumors, with lymphomas supplying the majority of the cases (1, 5).

Since the diagnosis of retroperitoneal lymphoma is so frequent a clinical problem, it commands special attention. In a considerable number of patients where the clinical evaluation suggests the presence of retroperitoneal node involvement with lymphoma, even the experienced clinician may be unable to delineate the nodes with reasonable certainty. Because the decision in regard to the most dynamic form of radiation therapy depends largely on the exact localization of the tumefactions, the radiologist is usually called upon for aid. He has at his command many procedures of varying technical ease and accuracy: plain roentgenography of the abdomen, laminagraphy, either vertical or horizontal, and a multitude of contrast studies such as intravenous pyelography, gastrointestinal studies, angiography, lymphography (8, 13, 14, 16), and retroperitoneal pneumography (2). According to the size and location of the involvement, one or another of these methods may be especially suited to the problem at hand. The first choice falls to the procedures that are simplest to perform, with the least discomfort to the patient.

We were impressed by the many characteristics of the inferior vena cava that make it suitable for demonstrating retroperitoneal masses. It is of a large uniform caliber, passing from the pelvis to the diaphragm, is flexible, and is in close relation to the lymph nodes. This gives it certain advantages over the ureters, which are more variable in their size and course and are not so intimately related to the lymph nodes.

The roentgenographic demonstration of the inferior vena cava was reported as early as 1935 by dos Santos (3). Since that time, there have been further reports by O'Loughlin (12), Helander (6, 11) and Kaufman (7). Methods utilized for demonstrating the vessel include bilateral percutaneous injection into the femoral veins, bilateral percutaneous femoral vein catheterization by the Seldinger method, and translumbar injection. It was our purpose to investigate the intraosseous route. One could inject contrast material into the femoral trochanters or the pelvis, but adequate outlining of the vena cava *via* these sites would require bilateral injection. Fischgold (4), Tori (15), and Lessmann (9) have shown that injection of opaque medium into the spinous process of a vertebra allows visualization of the vertebral plexuses and the inferior vena cava. We know from both anatomic and radiographic studies that these plexuses in the lumbar region are in free communication with the inferior vena cava. Thus, the spinous process of a lower lumbar vertebra affords a satisfactory solitary injection site.

Contrast medium introduced into the medullary canal of a lumbar spinous process will demonstrate the inferior vena cava through the vertebral plexus which communicates with it *via* the lumbar veins or will pass up the ascending lumbar veins

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into the azygos system. The physiology of the circulation in this region is closely related to the intra-abdominal pressure. Any straining by the patient or tightening of the abdominal muscles increases pressure in the abdomen and tends to keep the contrast medium within the vertebral plexuses so that it travels upward to the level of the thorax and then enters into the azygos system. Decreased intra-abdominal pressure encourages flow of the contrast medium into the vena cava. Aids in the production of this decreased pressure are careful explanation of the procedure to the patient, adequate premedication, and encouragement of deep inspiration at the time of the injection.

It is the purpose of this paper to report our experiences with intraosseous cavography in evaluating the retroperitoneal space and to compare the results with those of intravenous pyelography.

MATERIAL AND METHOD

Thirty-four patients with proved lymphoma and possible involvement of the retroperitoneal nodes were examined by both intravenous pyelography and intraosseous venography so that comparisons between the two methods could be made. Four of the positive cases were re-evaluated after treatment, giving a total of 38 studies. We also had the advantage of autopsy in 15 instances. In 10, the interval between necropsy and examination was sufficiently close that comparative findings could be presumed to be significant.

The examination is carried out in the following manner. A bone-marrow set, with Lundy-Irving needles, No. 16, and four syringes of 2 ml., 10 ml., 20 ml., and 30 ml. size, is utilized. The usual precautions regarding sensitivity to iodine are taken, and the patient should preferably be in a fasting state. The procedure is carefully explained to him, since full cooperation is necessary for a satisfactory study. Adequate premedication is essential. For the average patient, we give Demerol, 100 mg., Pyribenzamine, 25 mg. by intramuscular injection, and Seconal, 100 mg. orally, approximately half an hour before the injection. With the patient in the lateral recumbent position, under local anesthesia, the bone-marrow needle is inserted into the center of the medullary cavity of the spinous process of L-5 or L-4. The location is confirmed by the aspiration of marrow (which may be used for microscopic study) and by the test injection of a few cubic centimeters of 50 per cent Hypaque and a preliminary film. Twenty to twenty-five cubic centimeters of 50 per cent Hypaque is then injected manually as rapidly as possible. The patient is encouraged not to strain but to breathe in slowly and deeply so as to encourage adequate flow of the contrast medium through the vertebral plexus into the lumbar veins and the inferior vena cava. Two films are taken in rapid succession, with manual exchange of the cassettes. If there is adequate outlining of the inferior vena cava, the patient is rolled into a prone position and the injection is repeated. An outline of the inferior vena cava is thus obtained in both the lateral and the postero-anterior projections. Delayed films may be taken for outlining the collecting systems.

TOXICITY CONTROL

The experimental work of Wild (17), who injected contrast medium into the bone marrow of dogs, showed that injection into the same area on two different occasions did not produce pathologic findings. More frequent injections may be followed by a local inflammatory reaction. The trabecular structure of the bone may show some changes, but these undergo spontaneous healing. Potential complications such as thrombophlebitis, delayed hemorrhage, fever, local infection, embolism, and hypersensitivity reactions have not been encountered in our experience. Most patients complain of some pain of pressure type during the injection, persisting for several minutes and then gradually disappearing. The pain seems to vary inversely with the size and vascularity of the medullary cavity. A more burning type

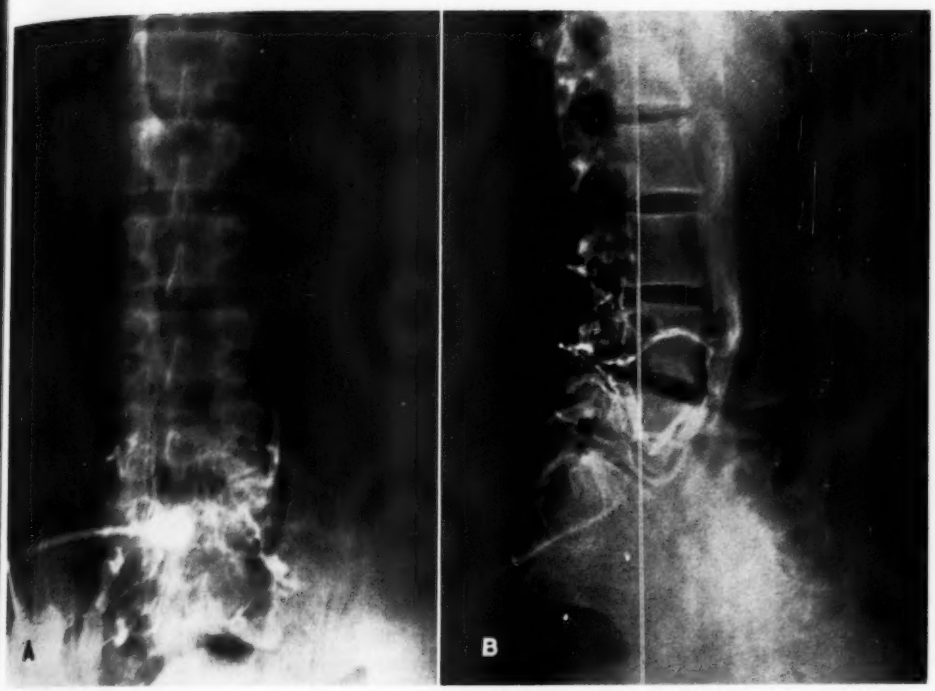

Fig. 1. Normal intraosseous cavograms. A. Postero-anterior view. B. Lateral view.

occurs when there has been some leakage of contrast medium about the needle and into the subcutaneous tissues. This is usually due to an initial unsuccessful attempt at placing the needle in the medullary cavity. The pain persists for fifteen to thirty minutes, but no complications have resulted from such leakage.

Contraindications to this procedure include hypersensitivity to either the local anesthetic or the contrast medium, local infection in the region of the injection site, and bone-marrow sclerosis or infiltration. These last contraindications are included since they make adequate outlining of the vena cava impossible.

FINDINGS

The normal findings and anatomic considerations have been clearly described by Helander and Lindbom (6). Some of the more pertinent points will be reviewed here.

The inferior vena cava is formed to the right side of L-5 by the junction of the two common iliac veins and may show a slight compression in this area from the right common iliac artery. The course is upward, to the right of the aorta, along the vertebral column. The left margin is usually 0.5 to 1 cm. to the right of the midline, and the right margin, which is slightly convex, is about the same distance lateral to the vertebral bodies (Fig. 1, A), to which the posterior margin is intimately related (Fig. 1, B). The diameter is quite constant to the level of the renal veins, where it increases slightly. There may be a slight impression on the posterior wall in this area from the right kidney. Above this level, the vena cava usually passes slightly forward through a groove in the posterior surface of the liver and penetrates the diaphragm, although in some cases it remains in apposition to the lumbar vertebrae.

The inferior vena cava is intimately related to the right retroperitoneal lymph nodes, some lying posteriorly, some to the left, and some anteriorly. On this basis, one can expect either displacement of

Fig. 2. Lateral cavogram showing diffuse narrowing in the lumbar region from pressure by a retroperitoneal lymphoma.

the vessel anteriorly to the right or narrowing from pressure along its anterior surface.

The diagnostic value of intraosseous cavography was compared to that of intravenous pyelography in 34 patients with lymphoma. In 21 cases there was displacement and/or narrowing of the inferior vena cava as the result of extrinsic pressure (Fig. 2). An associated finding sometimes seen was displacement or lack of filling of the lumbar veins. Developmental variations are common in these vessels, however, and interpretation from a solitary finding would be hazardous. In only 7 of these patients were changes noted on intravenous pyelography (Table I). The intraosseous venographic studies were positive in 12 cases in which pyelography was either negative or failed to outline the ureters satisfactorily. In 4 of these cases,

TABLE I: COMPARATIVE DIAGNOSES BY INTRAVENOUS PYELOGRAPHY AND INTRAOSSEOUS VENOGRAPHY IN 38 CASES (34 PATIENTS; REPEAT STUDY AFTER TREATMENT IN 4)

	Intravenous Pyelography (No. of Injections)	Intraosseous Venography (No. of Injections)
Positive	7	21
Negative	18	9
Questionable	8	3
Unsatisfactory	5	5
TOTAL	38	38

the level of displacement was above the level of the kidneys (Fig. 3); in the remaining 8, the nodes were either large enough to cause detectable changes in the vena cava, but not in the ureters, or were more intimately related to the vena cava.

Intravenous pyelography was positive in the presence of unsatisfactory intraosseous venograms in only 4 cases. The reasons for the unsatisfactory intraosseous study were inadequate outlining of the vena cava due either to straining by the patient or to bone-marrow infiltration; in 1 case there was displacement of the left lower ureter, an area not outlined on the cavogram (Table II). As to the certainty of the diagnosis, 8

TABLE II: PATIENT FINDINGS IN COMPARATIVE STUDIES BY INTRAOSSEOUS VENOGRAPHY AND INTRAVENOUS PYELOGRAPHY

	No. of Patients
Intraosseous venography positive; intravenous pyelography negative or unsatisfactory	12
Intravenous pyelography positive; intraosseous venography negative or unsatisfactory	5
Both examinations negative	5
Both examinations positive	9
Both examinations questionable	3
TOTAL	34

of the intravenous pyelograms were questionably positive, as compared to 3 of the intraosseous venograms.

The 10 patients who came to autopsy within a few months of the examination provided further information. In the presence of nodes 2 cm. or more in diameter, there were 1 questionably positive and 6 definitely positive cavograms whereas there were 3 false negative intravenous pyelograms (Table III). Nodes smaller

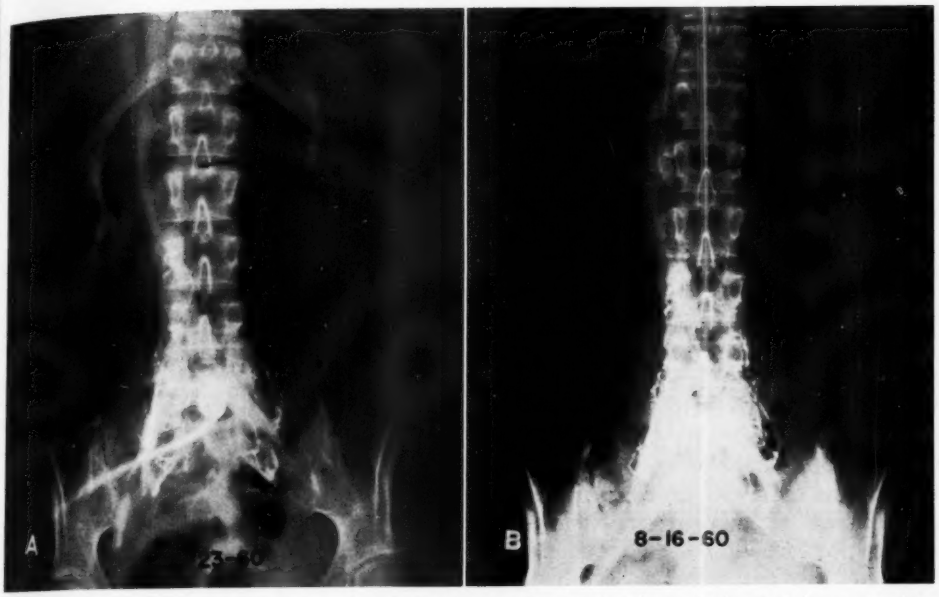

Fig. 3. A. Postero-anterior cavogram showing displacement and narrowing above the level of the renal pelvis. B. After treatment.

TABLE III: CORRELATION OF AUTOPSY EXAMINATION, INTRAVENOUS PYELOGRAPHY, AND INTRAOSSEOUS VENOGRAPHY IN 10 CASES

Case No.	Intravenous Pyelography	Intraosseous Venography	Autopsy
1	+?	+	Nodes 2 cm. or larger
2	+?	+?	Nodes 1 to 3.5 cm.
3	+?	U*	Nodes not enlarged
4	−	+	Nodes more than 2 cm.
5	U*	+	Nodes 2 to 4 cm.
6	−	+	Nodes 2 cm.
7	−	−	Nodes less than 1 cm.
8	−	−	Nodes less than 2 cm.
9	+	+	Nodes to 4 cm.
10	−	+	Nodes 2 cm.

*U. Unsatisfactory.

than 2 cm. were not demonstrated by either method. Another point of interest disclosed by autopsy findings was that in 2 of the cases with unsatisfactory cavograms there was extensive bone-marrow infiltration by tumor. This explains the difficulty of injection in these instances.

DISCUSSION

Other investigators have successfully utilized cavography in the demonstration of retroperitoneally expanding processes, but no comparisons with intravenous pyelography were undertaken. Helander and Lindbom (6) in 1956 reported a series of 55 cases with 16 abnormal cavograms in a variety of retroperitoneal lesions, with autopsy confirmation in 3. More recently, in 1959, they reported their entire experience with inferior vena cava venography. Notter and Helander (11) performed cavography in 33 patients with testicular tumors; findings were positive in 14 cases, 12 of which were proved at surgery. These and other investigators (7, 12) have chiefly employed bilateral percutaneous injection into the femoral veins either directly or *via* a catheter. Because of the bilateral direct injection and the larger amount of contrast medium, a sharper contrast of the vena cava was obtained than with a single injection into a lumbar spinous process. Diagnostic accuracy, however, has not suffered from this difference in contrast. Since the vena cava fills through a number of lumbar vessels, there is good mixing with the blood, and the borders of the vessels are clearly defined.

The intraosseous method of outlining the inferior vena cava has proved successful. Failures have been due to bone-marrow infiltration or straining on the part of the patient. The latter is usually the result of inadequate premedication.

Comparisons with intravenous pyelography show that cavography is a more accurate procedure for demonstrating retroperitoneal lymphoma. This seems to be due chiefly to the fact that the vena cava is larger and more constant in caliber than the ureters, follows a uniform course, and is more intimately related to the nodes, so that lymph node enlargement of a lesser degree is detected. In a few cases, also, displacement of the vessel was above the level of the kidneys. Since the vena cava lies in the right retroperitoneal space, cavography will obviously be of little help in the detection of small lesions limited to the left retroperitoneum. The disadvantages are the more involved technical procedure and some discomfort to the patient. For these reasons, the procedure should be reserved for cases where simpler methods have failed. On the basis of our autopsy findings, it can be stated that, as with all indirect methods, the nodes must be of a certain size before they can be demonstrated. With intraosseous cavography, we were not able to demonstrate nodes smaller than 2 cm. in diameter, but this was still superior to the results obtained by intravenous pyelography.

SUMMARY

Visualization of the inferior vena cava by intraosseous injection of contrast media has proved helpful in evaluating retroperitoneal adenopathy in patients with lymphoma. Analysis of the 34 cases investigated by both intraosseous cavography and intravenous pyelography showed that cavography could give more accurate information and its use should be considered when simpler methods fail to localize the retroperitoneal node involvement.

REFERENCES

1. CORBETT, R. S.: Retroperitoneal Tumours: Some Clinical Aspects. Clin. Radiol. **11:** 83–84, April 1960.

2. DAVIDSON, J. K., HAVARD, C. W., AND SCOTT, R. B.: Radiological Demonstration of Enlarged Retroperitoneal Lymph-Nodes. Lancet **1:** 1008–1010, May 16, 1959.

3. DOS SANTOS, R.: Phlébographie d'une veine cave inférieure suturée. J. d'urol. **39:** 586–587, 1935.

4. FISCHGOLD, H., ADAM, H., ECOIFFIER, J., AND PIEQUET, J.: Opacification des plexus rachidiens et des veines azygos par voie osseuse. J. d'radiol. et électrol. **33:** 37, 1952.

5. HARPER, R. A. K.: Radiology in the Diagnosis of Retroperitoneal Tumours. Clin. Radiol. **11:** 69–79, April 1960.

6. HELANDER, C. G., AND LINDBOM, Å.: Sacrolumbar Venography. Acta radiol. **44:** 410–416, November 1955. Roentgen Examination of the Inferior Vena Cava in Retroperitoneal Expanding Processes. Acta radiol. **45:** 289–297, April 1956. Venography of the Inferior Vena Cava. Acta radiol. **52:** 257–268, October 1959.

7. KAUFMAN, J. J., AND BURKE, D. E.: Abdominal Venography. Technique of Roentgen Visualization of the Inferior Vena Cava. Am. J. Roentgenol. **76:** 807–812, October 1956.

8. KINMONTH, J. B.: Lymphangiography in Man. Method of Outlining Lymphatic Trunks at Operation. Clin. Sc. **11:** 13–20, February 1952.

9. LESSMANN, F. P., SCHOBINGER VON SCHOWINGEN, R., AND LASSER, E. C.: Intra-Osseous Venography in Skeletal and Soft Tissue Abnormalities. Acta radiol. **44:** 397–409, November 1955.

10. MATHIS, C.: L'espace abdominal rétropéritoneal; étude anatomo-clinique. J. de chir. **79:** 299–306, March 1960.

11. NOTTER, G., AND HELANDER, C. G.: Über den Wert der Cavographie bei Diagnose und Behandlung retroperitonealer Testistumormetastasen. Fortschr. a. d. Geb. d. Röntgenstrahlen **89:** 409–417, October 1958.

12. O'LOUGHLIN, B. J.: Roentgen Visualization of the Inferior Vena Cava. Am. J. Roentgenol. **58:** 617–619, November 1947.

13. SHEEHAN, F. R., HRESHCHYSHYN, M., LIN, R. K., AND LESSMANN, F. P.: The Use of Lymphography as a Diagnostic Method. Radiology **76:** 47–53, January 1961.

14. TJERNBERG, B.: Lymphography as an Aid to Examination of Lymph Nodes; Preliminary Report. Acta Soc. med. upsal. **61:** 207–214, Nov. 30, 1956. Lymphography, Technique and Diagnostic Possibilities in Cases of Inflammation and Cancer Metastases. [In] Symposium, The IXth International Congress of Radiology, München, 1959. Stuttgart, Georg Thieme, 1961.

15. TORI, G.: The Radiological Demonstration of the Azygos and other Thoraco-Abdominal Veins in the Living. Brit. J. Radiol. **27:** 16–22, January 1954.

16. WELIN, S.: Lymphography: Development and New Techniques. [In] Symposium, The IXth International Congress of Radiology, München, 1959. Stuttgart, Georg Thieme, 1961.

17. WILD, H.: Intraossäre Phlebographie unter histologischer Kontrolle. Wien. klin. Wchnschr. **68:** 341–342, April 27, 1956.

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SUMMARIO IN INTERLINGUA

Un Studio Comparative de Cavographia Intraossee e Pyelographia Intravenose in le Demonstration de Lymphoma Retroperitonee

In un studio comparative del meritos de pyelographia intravenose e venographia intraossee in le demonstration de lymphoma retroperitonee, le autores ha usate ambe le methodos in le examine de 34 patientes con provate lymphoma e possibile affection del nodos retroperitonee. Quatro del positive casos esseva re-evalutate post le tractamento, resultante in un total de 38 studios. Necropsia esseva effectuate in 10 casos in que le intervallo inter le examine e le necropsia esseva sufficientemente breve pro justificar le supposition que le constatationes comparative esseva significative. Le injectiones intraossee esseva effectuate ad in le cavitate medullari del processos spinose de L5 o L4. Le substantia de contrasto usate esseva Hypaque (50 pro cento).

In 21 casos il habeva displaciamento e/o restringimento del vena cave inferior in consequentia de un pression extrinsec. In solmente 7 de iste casos, alterationes esseva notate in le pyelogrammas intravenose. Del altere latere, le venogrammas intraossee esseva positive in 12 casos in que le pyelogrammas esseva negative o exhibiva un inadequate delineation del ureteres. Le pyelogramma intravenose esseva positive in le presentia de un inadequate venogramma intraossee in solmente 4 casos. Octo pyelogrammas intravenose sed solmente 3 venogrammas intraossee esseva questionabilemente positive.

Le comparation demonstra que cavographia es le plus accurate inter le duo procedimentos in le demonstration de lymphoma retroperitonee. Isto pare esser principalmente le consequentia del facto que le vena cave es plus large e plus constante in calibre que le ureteres, que su curso es plus uniforme, e que illo es plus intimemente relationate con le nodos de maniera que minus marcate allargamentos de nodo lymphatic pote esser detegite. Le disavantages es le plus complexe technica e un certe grado de disconforto pro le patiente. Pro iste rationes le technica deberea esser reservate al casos in que plus simple methodos ha remanite sin successo. Super le base del constatationes necroptic, il es apparente que—de accordo con lo que vale pro omne methodos indirecte—le nodos debe haber un certe largor ante que illos pote esser demonstrate. Nodos de un diametro de minus que 2 cm non esseva demonstrate—sia per cavographia, sia per pyelographia.

A Comparative Experimental Approach to Contrast Materials in Renal Angiography[1]

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TRANSLUMBAR aortography and selective renal angiography are established diagnostic procedures that have grown apace with developments in vascular and renal surgery. When performed properly, they should be followed by few or no complications. They are, however, not entirely without hazard. Several years ago, McAfee (1), collecting statistics from across the country, reported on 13,207 abdominal aortograms, with renal complications in 0.37 per cent. More than 15 deaths due to nephropathy consequent to these procedures have been reported in the literature. Certainly many more unreported cases have occurred. It is logical to believe that renal damage following aortography is related to the initial sweep of contrast material through the kidneys. Subsequent renal passage of the medium should carry no more risk to the kidney than does an intravenous pyelogram.

Clinical experience has suggested that some of the commonly available contrast materials used in aortography endanger the kidneys more than others. With this in mind, it was decided that a comparative study of some of these media under experimental conditions would emphasize any advantage that might be gained by using a particular material. In the approach to this problem, there are many facets that deserve consideration, some of which are outlined in Diagram 1. The emphasis in this initial study was placed on the amount of the medium that actually passes through the kidney in a single circulation after renal artery injection, qualitative and quantitative changes in the nephrographic phase of renal angiography, and histologic changes in the kidneys resulting from

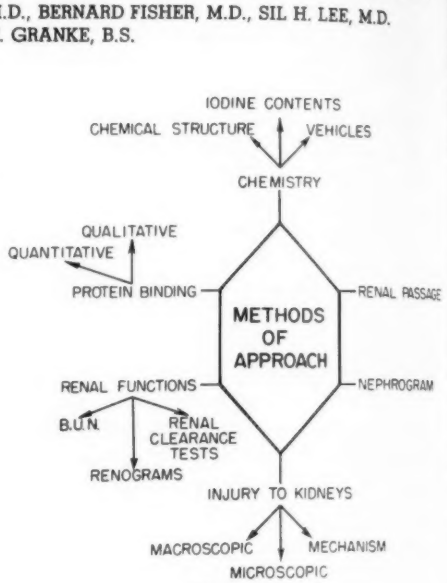

Diagram 1

injections of each of the materials under consideration. The other facets outlined in the diagram are touched upon only in theory.

METHOD

Four different contrast materials were studied. The trade names by which they are best known will be utilized. The chemical nomenclature and the formula for each are given in Diagram 2. Diodrast, the only diiodo compound used in this investigation, was employed in both 35 and 70 per cent concentrations; 70 per cent Urokon, 50 per cent Hypaque, and 60 per cent Renografin were also used. Healthy mongrel dogs (11 to 20 kg.) with normal blood urea nitrogen values were anesthetized with intravenous Nembutal in a mannitol solution. Blood pressure was monitored through a cannula in the right carotid artery. Following induction of anesthesia, a midline abdominal incision

[1] From the Departments of Radiology and Surgery, and the Laboratory of Experimental Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Penna. Presented at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960.

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was made exposing the left kidney, which was mobilized along with the renal artery, renal vein, and ureter. A polyethylene catheter was introduced through the femoral artery and guided under direct vision into the left renal artery. A pouch of inferior vena cava was created at the site where the left renal vein empties into this structure and a catheter was placed in this pouch to collect the venous blood. The ureter was divided and cannulated for the collection of samples of urine.

Each of the contrast materials was tagged with I^{131} and was injected in 10 c.c. amounts directly into the left renal artery. Injection times were constant, averaging from six and one-half to eleven and one-half seconds (Table I). A film of the kidney was exposed immediately after injection and at varying intervals up to five minutes. The renal vein blood was collected at ten-second intervals for one-hundred seconds, in standard wax cartons of cylindrical design. At the end of the procedure, the kidney was removed, stripped of the renal artery, renal vein, and

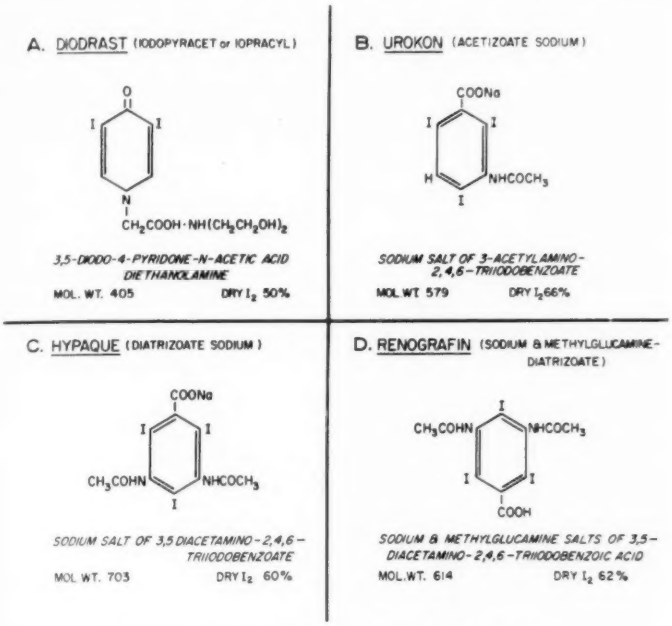

Diagram 2. Contrast materials employed in study.

TABLE I: MEAN VALUES FOR A FIVE-MINUTE PERIOD FOLLOWING THE COMPLETE INJECTION OF 10 C.C. OF CONTRAST MEDIUM INTO THE LEFT RENAL ARTERY

Contrast Material	Wt. of Dog (kg.)	Duration of Injection (sec.)	Drop in Systolic Blood Pressure (mm. Hg)	Per Cent Retained in Kidney	Per Cent in Collected Urine	Vol. of Collected Urine (c.c.)	Per Cent in Collected Blood	Vol. of Collected Blood (c.c.)
Diodrast (35%) (5 dogs)	13.0	8.0	23	16.6	2.7	7	75.9	166.0
Renografin (60%) (5 dogs)	16.7	11.5	29	8.2	0.9	8	74.9	405.0
Hypaque (50%) (5 dogs)	16.9	7.2	44	9.6	1.0	9	89.4	365.5
Urokon (70%) (5 dogs)	15.4	9.0	42	42.0	1.7	9.8	57.4	353.0
Diodrast (70%) (4 dogs)	15.1	6.5	53	15.1	2.6	7	83.9	330.5

ureter, and immersed in sufficient saline to cover its upper surface. The kidney, the collected blood and urine, and catheter washings were counted under standard conditions, utilizing a Reed-Curtis medical spectrometer and scaler unit with a well shielded sodium iodide scintillation crystal detector. The geometry was kept constant for each experiment. Counts were compared against a prepared standard containing the same total activity as was introduced into the renal artery. At the end of the acute experiment, the kidneys were removed and subjected to gross and microscopic examination.

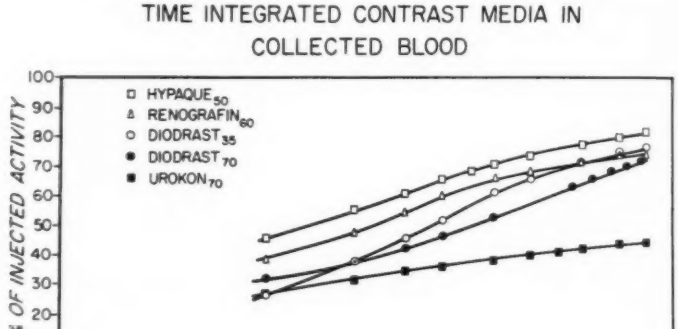

Diagram 3

In a second set of experiments, a renal artery injection was carried out in the same fashion, but the vein and ureter were not divided or cannulated and the dogs were allowed to recover. They were later sacrificed at varying intervals for study of the delayed effects of the contrast materials on the kidney parenchyma.

The nephrograms resulting from both sets of experiments were analyzed for qualitative differences, and planimetric measurements of the opacified kidneys were made for each of the materials at the different intervals.

RESULTS

The major findings of this study are presented in Table I. A fall in systolic blood pressure averaging 38 mm. of mercury occurred in the course of the acute experiment. No pressure, however, fell below a level of 60 mm. of mercury at the end of five minutes and in most instances the terminal figure was considerably above this level, suggesting that there was sufficient pressure to maintain an adequate renal blood flow (2). The average blood flow as measured by the volume of collected blood in the renal vein, however, amounted to only about 60 to 80 per cent of expected normal values (119 c.c./min./kidney) (3), except in the 35 per cent Diodrast group, where it was lower. This discrepancy may be related to the moderate fall in arterial pressure, intrarenal arterial spasm, and loss of negative pressure in the renal vein.

There was little variation among the tested media in the percentage of initial injected activity passing over into the collected urine. The volume was as expected for this time interval (2). Most significant, however, were the findings related to the percentage of injected activity retained in the kidney at the end of five minutes and the percentage of injected activity that had passed through the kidney into the renal vein blood in this interval. Table I shows that 70 per cent Urokon stands distinctly apart from the other tested materials. A considerably greater amount of this compound was retained within the kidney and a corre-

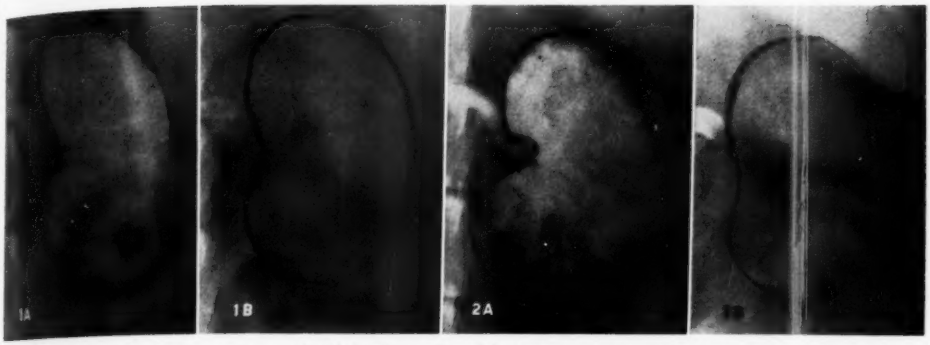

Fig. 1. A. Diodrast 35 per cent; end of injection. B. Diodrast 35 per cent; 90 seconds after completion of injection.

Fig. 2. A. Renografin 60 per cent; end of injection. B. Renografin 60 per cent; 60 seconds after completion of injection.

spondingly smaller percentage passed into the blood of the renal vein.

In some dogs, the factor of re-circulation had to be considered in spite of the experimental design, since sampling of the peripheral venous blood showed a count several times above background. This evidently resulted from collateral venous channels in the capsular area and, when present, negated the results obtained with that kidney.

An expression of the time-integrated accumulation of the media in the renal blood in the first one-hundred seconds is presented in Diagram 3. The rather flat curve of Urokon accumulation attests to the relative tenacity with which the kidney appears to "hold on" to this material and correlates well with the nephrograms obtained in this study.

Injection of 35 per cent Diodrast produced a uniform and homogeneous nephrogram in the early phases, which allowed for ready distinction of the corticomedullary junction, but in each study the nephrogram became faint to absent within one minute (Fig. 1, A and B). Injection of 60 per cent Renografin gave a reasonably homogeneous nephrogram (Fig. 2, A and B). Here, as with 35 per cent Diodrast, the major vessels were faintly visible both in the initial phases (opaque) and in the later nephrographic phase (non-opaque). By the end of one minute, 4 out of 5 of the Renografin kidneys showed only a trace of residual contrast material remaining in the kidney. The nephrogram obtained with 50 per cent Hypaque was similar to that obtained with 60 per cent Renografin with only faint to moderate opacity remaining at sixty seconds (Fig. 3, A and B).

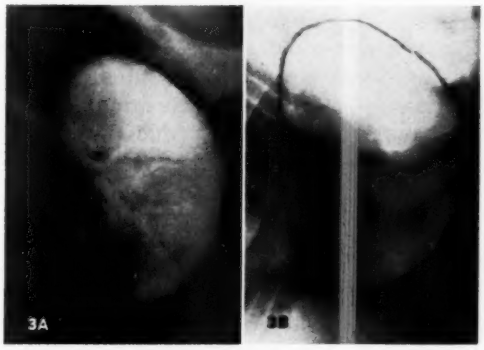

Fig. 3. A. Hypaque 50 per cent; end of injection. B. Hypaque 50 per cent; 40 seconds after completion of injection.

Injection of 70 per cent Diodrast produced a densely opacified kidney in which one could not distinguish the renal vessels from the remainder of the parenchyma and the corticomedullary border was obliterated. Films obtained at ninety to three-hundred seconds after the completion of the injection all showed irregular patches of contrast material (Fig. 4, A and B). Injection of 70 per cent Urokon produced the most profound nephrogram, with an initial diffuse, homogeneous, deep opacity which in 4 of 6 cases remained of almost the same intensity for films taken

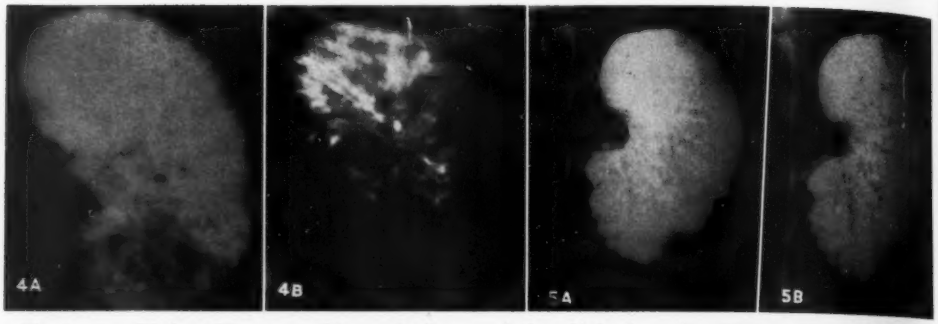

Fig. 4. A. Diodrast 70 per cent; 60 seconds after completion of injection. B. Diodrast 70 per cent; 300 seconds after completion of injection.
Fig. 5. A. Urokon 70 per cent; 70 seconds after completion of injection. B. Urokon 70 per cent; 300 seconds after completion of injection.

up to five minutes (Fig. 5, A and B). No clear-cut corticomedullary junctions were observed nor could the vessels be demarcated. This considerable retention of opacity at the end of five minutes was directly related to the large amount of contrast material retained in the kidney (Table I).

Planimetric studies in which the surface area was mapped out for each of the interval films in all of the nephrograms also provided findings of interest. Diagram 4 demonstrates the contraction of the Urokon kidneys and the moderate dilatation of the kidneys injected with the other contrast materials that persists during the five minutes of study.

AVERAGE % CHANGE IN KIDNEY SIZE AFTER INJECTION OF CONTRAST MEDIA

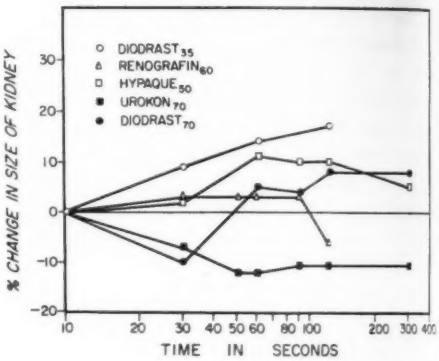

Diagram 4

HISTOLOGIC CHANGES

No early or late damage was demonstrated in the kidneys injected with 35 per cent Diodrast, 60 per cent Renografin, or 50 per cent Hypaque. Examination of the kidneys of dogs sacrificed five minutes after injection with 50 per cent Urokon and 70 per cent Diodrast showed areas of hemorrhage and coagulation necrosis situated predominantly on the cortical side of the corticomedullary junction. This change was noted in all of the Urokon-injected kidneys (Fig. 6) and in 50 per cent of those receiving 70 per cent Diodrast. The opposite or uninjected kidney showed no abnormality either grossly or on microscopic study. Two dogs with intact renal veins and intact ureters receiving 70 per cent Urokon died within twenty-four hours and each showed patchy areas of coagulation necrosis. Urokon-injected dogs sacrificed five, sixteen, and twenty-one days later showed gross lesions located in both the cortical and medullary portions of the kidney but predominantly in the cortex. Similar changes were found in 2 out of 4 70 per cent Diodrast kidneys at intervals of nine to twenty-one days (Fig. 7). The early changes noted on microscopic study in the 70 per cent Urokon and 70 per cent Diodrast groups consisted of swelling of the glomerular tufts and tubular lining cells, with karyolysis (Fig. 8). In some instances a granular proteinoid material was found in the capsular spaces and tubules. Almost complete cortical necrosis occurred in some areas in dogs sacrificed

at the end of one day after injection of 70 per cent Urokon (Fig. 9). Dogs sacrificed at intervals of five to twenty-one days showed focal areas of cortical necrosis and areas of severe atrophy of the tubules and glomeruli (Fig. 10), dilatation of the proximal tubules with vacuolization,

Fig 6. Cut section of kidney removed 5 minutes after completion of 70 per cent Urokon injection. Note areas of cortical necrosis.

and, in some instances, hyaline droplet formation in the epithelial tubular cytoplasm.

In several animals, India ink was injected along with the contrast material. No evidence of extravasation was present in the kidneys injected with Urokon or with Hypaque (Fig. 11). Similar studies were not carried out for the other contrast materials.

It is apparent from the evidence cited above that, under the conditions of this experiment, 70 per cent Urokon and 70 per cent Diodrast produced the most profound changes in the parameters measured. This was particularly true of Urokon, which caused sustained contraction of the kidney, tended to remain in the kidney in larger amounts than other contrast materials, passed into the renal venous blood in smaller amounts, and uniformly led to varying degrees of necrosis. While 70 per

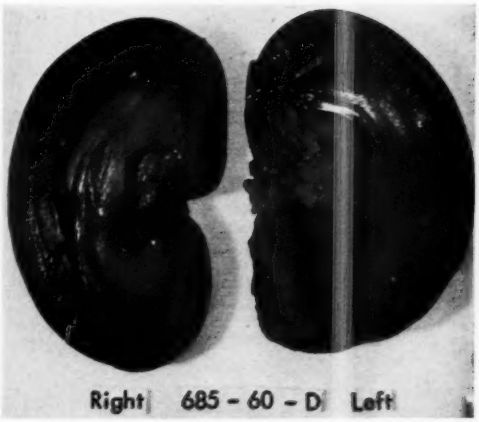

Fig. 7. Left kidney, removed 9 days after injection of 70 per cent Diodrast, shows cortical necrosis and medullary congestion. The uninjected right kidney is normal.

cent Diodrast gave rise to only an initial and transient contraction of the kidney, it also produced (in lesser degree) untoward histologic changes. These appeared to correlate with a persistent nephrographic stain at periods up to five minutes post-injection.

The apparent discrepancies between the persistent nephrographic effect and the percentages of the media retained in the kidney as determined by the radioactive iodine method can be explained when one recalls that 70 per cent Urokon contains approximately 46 per cent iodine in solution, 70 per cent Diodrast contains about 35 per cent, 50 per cent Hypaque contains 30 per cent, 60 per cent Renografin contains 29 per cent, and 35 per cent Diodrast contains 17.5 per cent. Thus, 10 c.c. of 70 per cent Urokon is equivalent to 4.6 gm. of iodine in solution, and 42 per cent of this, which was retained in the kidney at the end of five minutes, would amount to approximately 1.93 gm. of iodine. Correspondingly, with 70 per cent Diodrast, there would be 0.52 gm. of retained iodine at the end of five minutes and for 50 per cent Hypaque, 0.30 gm.; for 35 per cent Diodrast, 0.28 gm. and for 60 per cent Renografin, 0.23 gm. These iodine values closely correspond with the nephrographic effects at the end of five minutes.

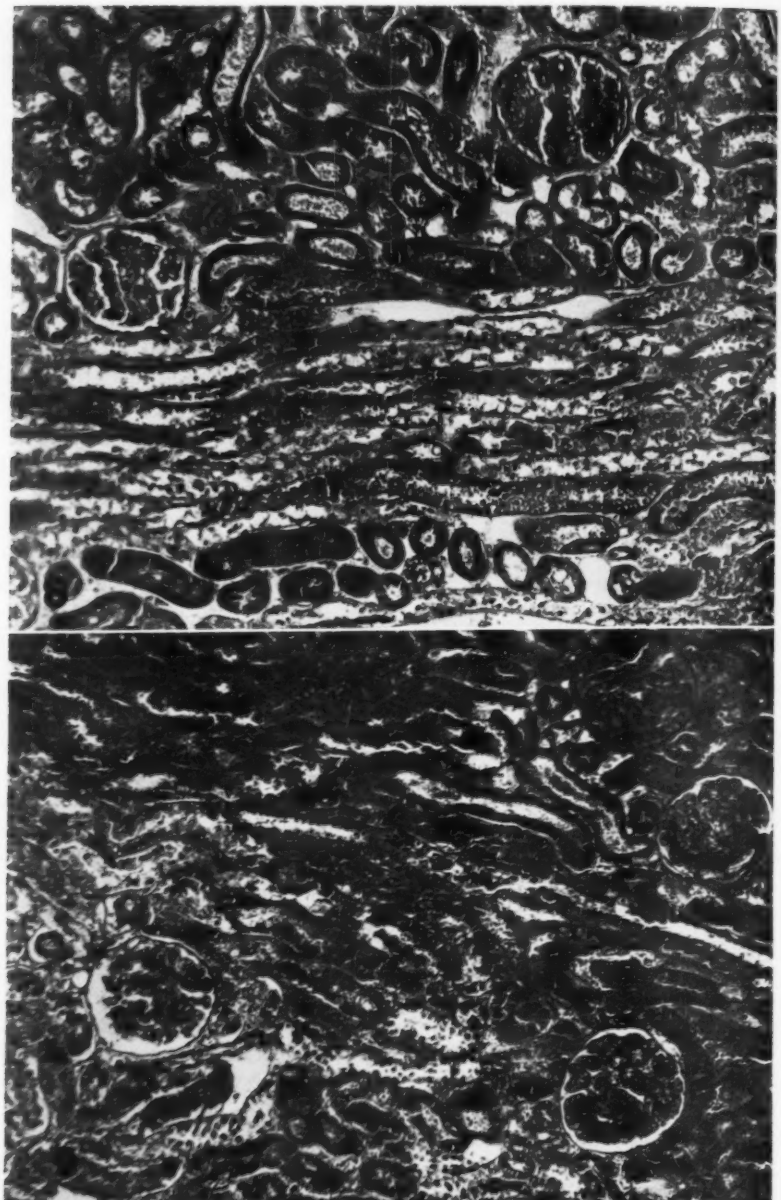

Fig. 8. Photomicrograph of kidney removed 5 minutes after injection of 70 per cent Urokon. Note karyolysis and swelling of glomerular and tubular cells.

Fig. 9. Photomicrograph of kidney one day after injection of 70 per cent Urokon. Note rather uniform cortical necrosis.

DISCUSSION

Since the employment of potentially toxic contrast materials in proximity to or within the renal artery appears to be increasing in radiologic practice, it is vital that information concerning any potential or actual advantage associated with the utilization of a particular medium be

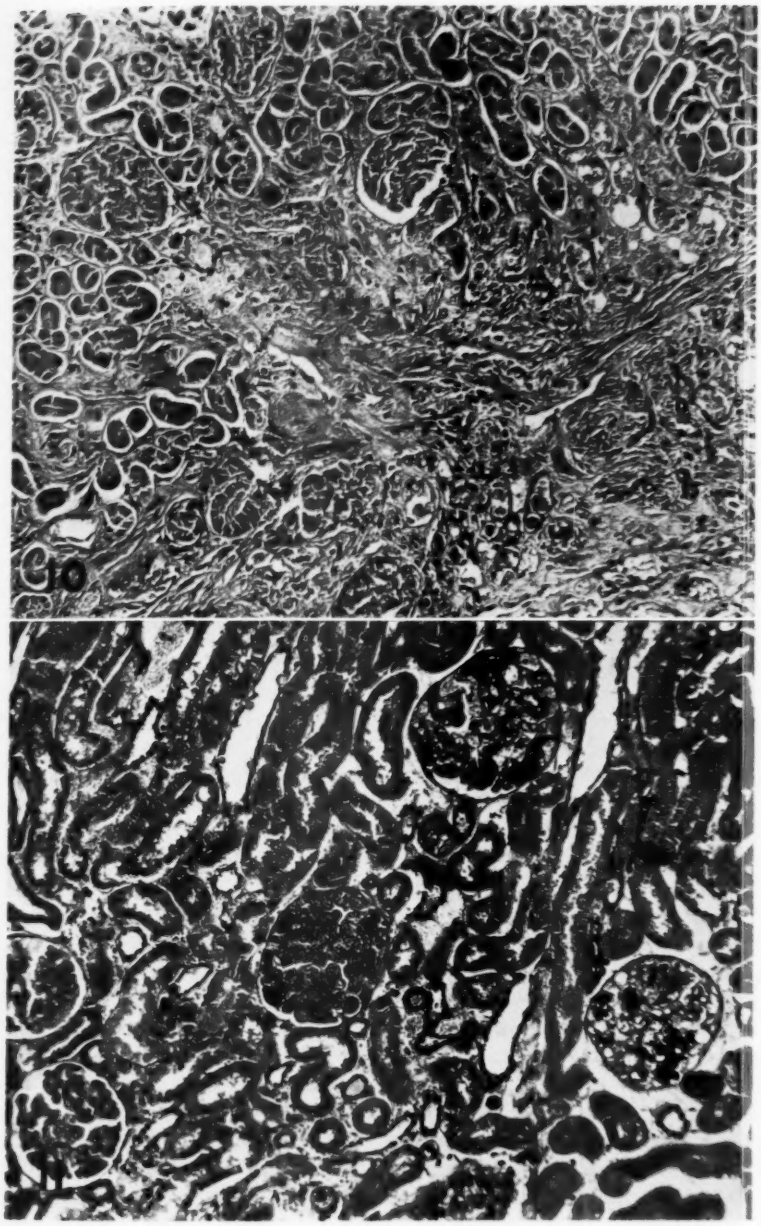

Fig. 10. Photomicrograph of kidney, 15 days after injection of 70 per cent Urokon. Note focal necrosis and atrophy.

Fig. 11. Section of kidney removed 5 minutes after combined injection of Urokon and India ink. No evidence of vascular rupture or extravasation.

obtained. The dosage schedules in this experiment were designed to provide a bolus of contrast material greater than that usually necessary to effect a satisfactory aortogram or renal angiogram in clinical practice. If one is forced to exceed recommended dosage schedules in clinical aortography, it is worthwhile

knowing that experimental evidence suggests a useful margin of safety with some contrast materials in contradistinction to others.

In the past eight to ten years, a number of interesting reports have appeared related to the general subject of the excretion of contrast materials, and particularly to the nephrographic effect in their passage through the kidney. In 1952 Josephson (4) discussed the general mechanism of excretion of renal contrast substances, pointing out that with Diodrast both tubular excretion and glomerular filtration increased proportionally to the plasma concentration as long as this was low (under 15 to 20 mg. per 100 c.c. in healthy persons). Tubular excretion, however, reached a maximum of 25 to 50 mg. per minute, which could not then be exceeded, and with very high plasma concentrations, such as would be found in excretory urography and certainly in aortography, filtration dominated over tubular excretion. Porporis and his coworkers (5) in 1954 found that with Urokon, plasma concentrations above 30 mg. per cent led chiefly to glomerular filtration. Under circumstances of clinical excretory urography with Urokon, levels of 100 to 300 mg. per cent are achieved, and it is obvious that the Urokon contributed by glomerular filtration will far exceed that contributed by the tubules. Josephson and Kallas (6) further dissected the mechanism of Diodrast tubular excretion and pointed out that, when a low or moderate amount of Diodrast is offered to the excretory cells of the kidney, the medium is transferred to the tubules without intracellular accumulation but when a certain limit is exceeded, Diodrast starts to accumulate in the cells in concentrations high enough to give an x-ray shadow by special x-ray absorption technics (7).

In a simple and cleverly contrived study, Edling and Helander (8) showed that the nephrographic effect in renal angiography consists of three stages: (*a*) an initial vascular phase, (*b*) tubular accumulation and excretion, and (*c*) a phase of back diffusion from the tubular cells into the veins in combination with tubular transport. Their description of the nephrogram appears worth repeating in its entirety. "The loss of the demarcation between cortex and medulla occurred when the contrast medium passed through the descending and ascending limbs of the pars recta of the tubules, the nephrographic effect being temporarily fairly homogeneous. The density in the cortex then faded due to a decrease in the concentration of the contrast medium in the proximal tubules, following elimination of fluid of high concentration and the addition of a glomerular filtrate of much lower concentration. In addition, the tubular cells lose contrast medium from back diffusion into the blood and from excretion into the tubular ducts. Hence the pyramids and finally the papilla have the highest density, indicating that the contrast medium has reached the collecting ducts. The nephrographic effect is finally lost with the emptying of the tubular ducts into the pelvis."

In a more comprehensive study (9), Helander has written extensively on his findings in experimentally produced renal damage following injection of contrast material. Working with Urografin, Miokon, and Umbradil, he produced microscopic injuries in the kidneys of 14 of 22 dogs following direct injection into the renal artery. The injuries varied in degree and extent, with diffuse lesions being localized chiefly to the outer parts of the cortex, often with small superficial infarctions. Tubular injuries, mainly involving the proximal parts of the nephrons, occurred in the majority of cases. Helander did not feel that they related to the hypertonicity of the contrast media and concluded that, in general, a normal appearing angionephrographic effect was unlikely to be associated with any serious morphologic change. However, abnormal angionephrographic effects (persistence of the arterial phase, abnormal prolongation of the nephrographic effect in the cortex, and ragged, irregular accumulations of the

contrast material) were invariably attended by pronounced morphologic change and functional disturbance. Helander furthermore was of the opinion that the contrast concentration *per se* was not sufficient to explain the unpredictable variations in renal parenchymal damage.

Similarly, Idbohrn and Berg (10) concluded that there was an absence of any definite relationship between the severity of renal injury and the concentration of injected contrast material in studies carried out in rabbits. Their predominant renal injury was a severe but transient disturbance of the permeability of the glomeruli with exudation of plasma proteins in the tubules. In a later study, Idbohrn along with Berg and Wendeberg (11), again with rabbits, found that retrograde aortic injections of Hypaque varying in concentration between 45 and 90 per cent and Urografin in 22.5 and 76 per cent concentrations, caused no demonstrable renal damage, but that changes were associated with similar injections of Urokon (17.5 and 37.5 per cent) and Miokon (25 to 50 per cent).

Beall and his co-workers (12) in this country, in a clinical and experimental study, concluded that the immediate renal hemodynamic response to injection of Urokon is vasoconstriction. This appeared to depress both the glomerular filtration rate and the renal blood flow. These workers found that a third of their patients receiving more than 35 c.c. of 70 per cent Urokon in the course of aortography suffered a depression of glomerular filtration rate of more than 20 per cent in twenty-four to forty-eight hours. About the same time, Huger, Margolis, and Grimson (13) observed minor injuries to dog kidneys after injection of 0.5 c.c. per kilogram of 70 per cent Urokon. The contrast material in this case passed selectively into both renal arteries. It was found that severe necrosis occurred after 1.5 and 2.0 c.c. per kilogram under these circumstances. There appeared to be some protection afforded by the prior injection of procaine. In a previous study (14) these investigators utilized a plethysmograph to show that Urokon and Diodrast in the concentrations employed produced a prompt and active decrease of volume in the kidney or renal vasoconstriction and reduced systemic blood pressure. In contrast, the plethysmographic studies with Hypaque and Miokon showed a prompt and somewhat passive dilatation of the kidney, with an increase of systemic blood pressure at the moment of injection. This supposedly resulted in increased flow, poor visualization, and lower toxicity.

Experimental studies designed to measure degrees of spasm in other vascular beds have shown similar findings. Vascular contraction occurred with Urokon and was absent with Renografin and Cardiografin, Hypaque, and Miokon (15, 16).

Our results, then, seem to be in accord with those reported in the literature. The intensity and duration of the nephrogram produced by the varying contrast materials under the conditions of our study appeared to relate rather well to the amount of iodine that remained in the kidney or passed on through into the renal vein blood as determined by counting procedures with radioactive tags. The planimetric studies suggest that vascular spasm may play a part in the rather marked retention of Urokon and 70 per cent Diodrast in contradistinction to the other media tested. It is conceivable, however, that vascular spasm is an incidental effect, since it occurred for only a transient period with 70 per cent Diodrast.

Previous workers have shown that osmotic effects and *p*H variations are not of primary importance in the production of macroscopic or microscopic changes, but there are other parameters that should be considered. Protein binding, for example, is an unexplored field and it is conceivable that there may be quantitative differences in the protein binding that takes place with the different contrast materials. This would certainly affect the glomerular filtration and the tubular excretion of these media. Preliminary

studies in this laboratory have indicated that protein binding may be instantaneous. Further work will be necessary to determine quantitative and qualitative differences in this respect. The chemical structure of the contrast material itself may be of some significance, but at present no data are available on this point.

In this study, 70 per cent Urokon and 70 per cent Diodrast, in high dosages, produced injuries to the kidney that were not duplicated by similar injection of 50 per cent Hypaque, 60 per cent Renografin, or 35 per cent Diodrast. Since both Renografin and Hypaque in the concentrations cited above will provide a satisfactory density for most clinical aortography or renal angiography, it is suggested that these materials be used and that both Urokon and Diodrast in 70 per cent concentrations be discarded for any aortic injection above the level of the renal vessels.

SUMMARY

1. An experiment was designed to test the effect on the dog kidney of a single passage of contrast material injected into the renal artery.

2. In comparison with the other contrast media tested, a larger percentage of 70 per cent Urokon was retained in the kidney and a correspondingly smaller amount passed into the renal vein.

3. In the immediate post-injection period of maximal opacification, 70 per cent Urokon appeared to cause a prolonged contraction of the kidney, 70 per cent Diodrast produced a transient contraction, while the other media appeared to cause slight dilatation of the kidney. Slight contraction of the Renografin kidneys occurred at a somewhat later stage, when the maximum concentration of the contrast material had cleared.

4. Injection into the renal artery of 70 per cent Urokon and 70 per cent Diodrast in relatively high dosage schedules led to both acute and chronic changes in kidney histology. These were more consistent after injection of Urokon. Injections of 50 per cent Hypaque, 60 per cent Renografin, and 35 per cent Diodrast failed to produce any histologic abnormalities either in the immediate post-injection phase or later.

5. The nephropathic effects of 70 per cent Urokon and 70 per cent Diodrast may be related to the resultant sustained exposure of kidney vessels to the contrast material. There are, however, unexplored facets that might also play a role in the production of nephropathy.

NOTE: The authors gratefully acknowledge the invaluable assistance of Dr. Robert Totten, who reviewed the pathology sections.

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REFERENCES

1. MCAFEE, J. G.: Survey of Complications of Abdominal Aortography. Radiology **68:** 825–838, June 1957.

2. BOUNOUS, G., SHUMACKER, H. B., JR., AND KING, H.: Studies in Renal Blood Flow, I. Some General Considerations. Ann. Surg. **151:** 47–58, January 1960.

3. SELKURT, E. E., HALL, P. W., AND SPENCER, M. P.: Response of Renal Blood Flow and Clearance to Graded Partial Obstruction of the Renal Vein. Am. J. Physiol. **157:** 40–46, April 1949.

4. JOSEPHSON, B.: The Mechanism of the Excretion of Renal Contrast Substances. Acta radiol. **38:** 299–306, October 1952.

5. PORPORIS, A. A., ELLIOTT, G. V., FISCHER, G. L., AND MUELLER, C. B.: The Mechanism of Urokon Excretion. Am. J. Roentgenol. **72:** 995–1003, December 1954.

6. JOSEPHSON, B., AND KALLAS, J.: Iodine Concentration in Rabbit Kidneys After Diodrast Injection; Mechanism of Renal Tubular Excretion. Am. J. Physiol. **174:** 65–71, July 1953.

7. ENGSTRÖM, Å., AND JOSEPHSON, B.: Historadiographic Demonstration of Diodrast in the Rabbit Kidney. Am. J. Physiol. **174:** 61–64, July 1953.

8. EDLING, N. P. G., AND HELANDER, C. G.: Nephrographic Effect in Renal Angiography. An Experimental Study in Dogs. Acta radiol. **51:** 17–24, January 1959.

9. HELANDER, C. G.: Nephrographic Effect and Renal Arteriographic Damage. An Experimental Study. Acta radiol. Suppl. 163, 1958.

10. IDBOHRN, H., AND BERG, N.: On the Tolerance of the Rabbit's Kidney to Contrast Media in Renal Angiography; A Roentgenologic and Histologic Investigation. Acta radiol. **42:** 121–140, August 1954.

11. BERG, N. O., IDBOHRN, H., AND WENDEBERG, B.: Investigation of the Tolerance of the Rabbit's Kidney to Newer Contrast Media in Renal Angiography. Acta radiol. **50:** 285–292, September 1958.

12. BEALL, A. C., JR., CRAWFORD, E. S., COUVES, C. M., DEBAKEY, M. E., AND MOYER, J. H.: Complication of Aortography. Factors Influencing Renal Function Following Aortography with 70 Per Cent Urokon. Surgery **43:** 364–380, March 1958.

13. HUGER, W. E., JR., MARGOLIS, G., AND GRIMSON, K. S.: Protective Effect of Intra-Aortic Injection of Procaine Against Renal Injuries Produced in Experimental Aortography. Surgery **43:** 52–62, January 1958.

14. THOMSON, H. S., MARGOLIS, G., GRIMSON, K. S., AND TAYLOR, H. M.: Effects of Intra-Arterial Injection of Iodine Contrast Media on the Kidney of the Dog. Arch. Surg. **74**: 39–49, January 1957.

15. MOE, R. A., AND CRAVER, B. N.: The Evaluation of Physiological Responses to Intra-arterial Administrations of Various Contrast Media. Ann. New York Acad. Sc. **78**: 894–903, July 2, 1959.

16. GUZMAN, S. V., AND WEST, J. W.: Cardiac Effects of Intracoronary Arterial Injections of Various Roentgenographic Contrast Media. Am. Heart J. **58**: 597–607, October 1959.

DISCUSSION

Herbert L. Abrams, M.D. (San Francisco, Calif.): I think this was a fine paper, but I believe we must emphasize the importance of a comparable concentration of the media if we are to draw any inferences with respect to contrast studies in clinical practice. In other words, comparing 70 per cent Urokon with 50 per cent Hypaque or Renografin is not an entirely satisfactory approach to the evaluation of these drugs. Furthermore, it is important to assess the toxicity of these agents in terms of a constant dose-weight relationship rather than in terms of an absolute volume.

Aside from these reservations, I think we should commend Dr. Lasser on his studies. We are all interested in the nephrotoxic effects of contrast media, and we are delighted to see these effects explored systematically and in detail.

SUMMARIO IN INTERLINGUA

Studio Experimental Comparative de Substantias de Contrasto in Angiographia Renal

In experimentos in canes le autores ha studiate le effecto, in le renes, de un unic passage de substantia de contrasto injicite ad in le arteria renal. Le sequente substantias esseva testate: Diodrast (in concentrationes de 35 e 70 pro cento), Urokon (70 pro cento), Hypaque (50 pro cento), e Renografin (60 pro cento).

In comparation con le altere substantias testate, un plus grande procentage de Urokon de 70 pro cento esseva retenite in le ren, e un correspondentemente plus reducite quantitate passava ad in le vena renal.

In le periodo immediatemente post le injection, durante que le opacification esseva a su maximo, Urokon de 70 pro cento pareva causar un prolongate contraction del ren; Diodrast de 70 pro cento causava un contraction transiente; e le altere substantias pareva causar un leve dilatation del ren.

Injectiones ad in le arteria renal de Urokon de 70 pro cento e de Diodrast de 70 pro cento in relativemente alte dosages resultava in acute e chronic alterationes histologic del ren. Iste effecto esseva plus uniforme post injectiones de Urokon. Injectiones de Hypaque de 50 pro cento, de Renografin de 60 pro cento, e de Diodrast de 35 pro cento non produceva ulle anormalitates histologic immediate- o tardivemente post le injection.

Viste que tanto Renografin como etiam Hypaque (in le supra-listate concentrationes) provide un satisfacente densitate pro le majoritate del problemas clinic de aortographia o de angiographia renal, le suggestion es presentate que iste duo materiales es usate e que tanto Urokon como etiam Diodrast in concentrationes de 70 pro cento es discartate pro injectiones aortic supra le nivello del vasos renal.

Effects of Intra-Arterial Injection of Miokon, Hypaque, and Renografin in the Small Intestine of the Dog[1]

TED GRAYSON, M.D., ALEXANDER R. MARGULIS, M.D., PETER HEINBECKER, M.D., and SIDNEY L. SALTZSTEIN, M.D.

INTESTINAL VESSELS were first made radiopaque by translumbar aortography. The contrast media employed in the early days were sodium iodide and iodopyracet (Diodrast). Necrosis and perforation of the small intestine occasionally attended their use. This was thought to be due either to the inherent toxicity of the medium or to its excess concentration (9). It was hoped that sodium acetrizoate (Urokon) would be less dangerous, but intestinal necrosis and deaths were reported following the injection of 70 per cent Urokon into the mesenteric arteries. When sodium diprotrizoate (Miokon), sodium diatrizoate (Hypaque), and methylglucamine diatrizoate (Renografin) became available, they were believed to be safer than sodium iodide, Diodrast, or Urokon. Lloyd (6) in comparative studies showed Hypaque to be less toxic than Miokon, and this was confirmed by Stokes (13) and Chaplin and Carlsson (1). Fischer and Eckstein (3) found fewer systemic effects with Renografin in cerebral angiography than with either Urokon or Hypaque. Hoppe (4) injected 50 per cent Hypaque into the marginal ear vein of rabbits with no tissue damage.

In spite of the reports of intestinal necrosis and perforation after the intra-arterial injection of contrast media, few detailed studies of their effects on the small bowel have been made. Various investigators have used the survival of patients or experimental animals as proof of the safety of such injections (10–12). Absence of catastrophic symptoms and survival, however, indicate only that complete necrosis with perforation of the intestine did not occur. Since mesenteric arteriography shows promise as a diagnostic aid (7, 8, 11, 12), we undertook a study of the effects of Miokon, Hypaque, and Renografin on the small intestine.[2]

METHOD

Full-grown, healthy male mongrel dogs weighing about 30 pounds were used. These animals were anesthetized with sodium pentobarbital, celiotomy was performed, and a loop of distal ileum was selected for injection. In many dogs more than one loop was used. The artery to the loop was then dissected free and cannulated with a 21-gauge scalp-vein needle. Great care was taken not to damage the adjacent vein. The selected contrast medium in various concentrations and dosages was injected rapidly by hand into the artery, and roentgenograms were obtained at the completion of the injection and three minutes later. When multiple loops were injected in the same dog, at least one interval artery and vein were left intact. Contraction of the loop of intestine during and after injection was observed and graded as 0 through 4+. Numerous control loops were either injected with 20 ml. of normal saline or the artery was ligated and nothing injected. Autopsies were done on the dogs that died. In all that survived, the injected loops were resected three weeks after injection. All segments were studied grossly and microscopically. The microscopic examination was performed by one of us (S. L. S.) without knowledge of the type of contrast medium, concentration, or volume injected. The roentgenograms were re-

[1] From the Department of Surgery and The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo. Presented at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960. Studies supported by U. S. Public Health Grant, A4397.

[2] The organic iodine content of 50 per cent Miokon and of 50 per cent Hypaque is roughly the same as that of 60 per cent Renografin.

Fig. 1. A. Mesenteric arteriogram obtained by injection of 8 ml. of Miokon into a loop of ileum of a dog. There is some extravasation of the medium into the wall of the gut. B. Photomicrograph of the injected bowel segment. The dog died after this segment became necrotic and the bowel perforated. There is complete necrosis of the intestinal wall, involving all layers. A thin layer of granulation tissue lines the lumen. Hematoxylin and eosin. ×75.

viewed independently (A. R. M.), and correlation of extravasation of contrast medium with histologic findings was attempted (Figs. 1–4).

RESULTS

Fifty-six ileal loops were studied; 10 were controls and 46 were injected with radiopaque material. Five control loops were injected with normal saline and in 5 the artery was ligated. No gross or microscopic changes were shown in any of the controls. In some loops injected with contrast medium, muscle necrosis, as evidenced

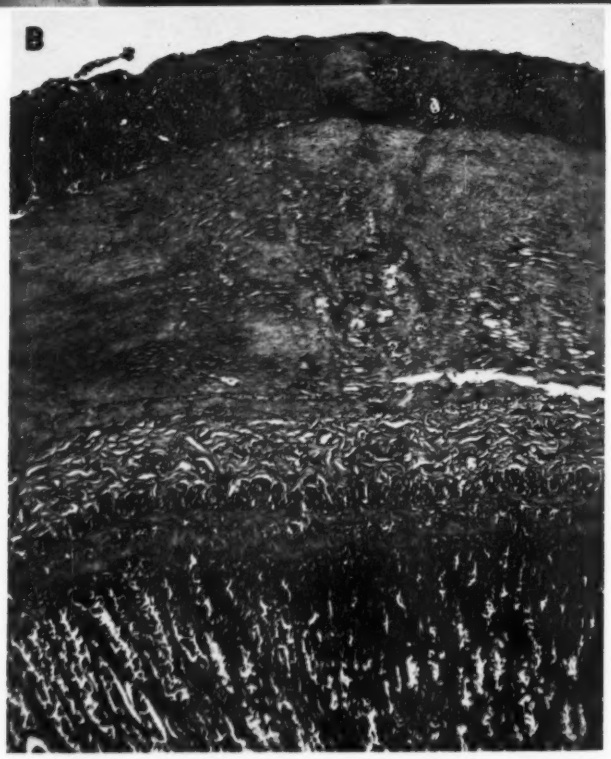

Fig. 2. A. Angiogram obtained by injection of 4 ml. of 50 per cent Miokon into the terminal mesenteric artery supplying a loop of the ileum of a dog. The angiogram is of good quality. No extravasation is seen. B. Microscopic section of the same loop following resection. There is patchy necrosis of the muscularis evidenced by focal loss of nuclear staining and homogenization of muscle fibers. Hematoxylin and eosin. × *c.*55.

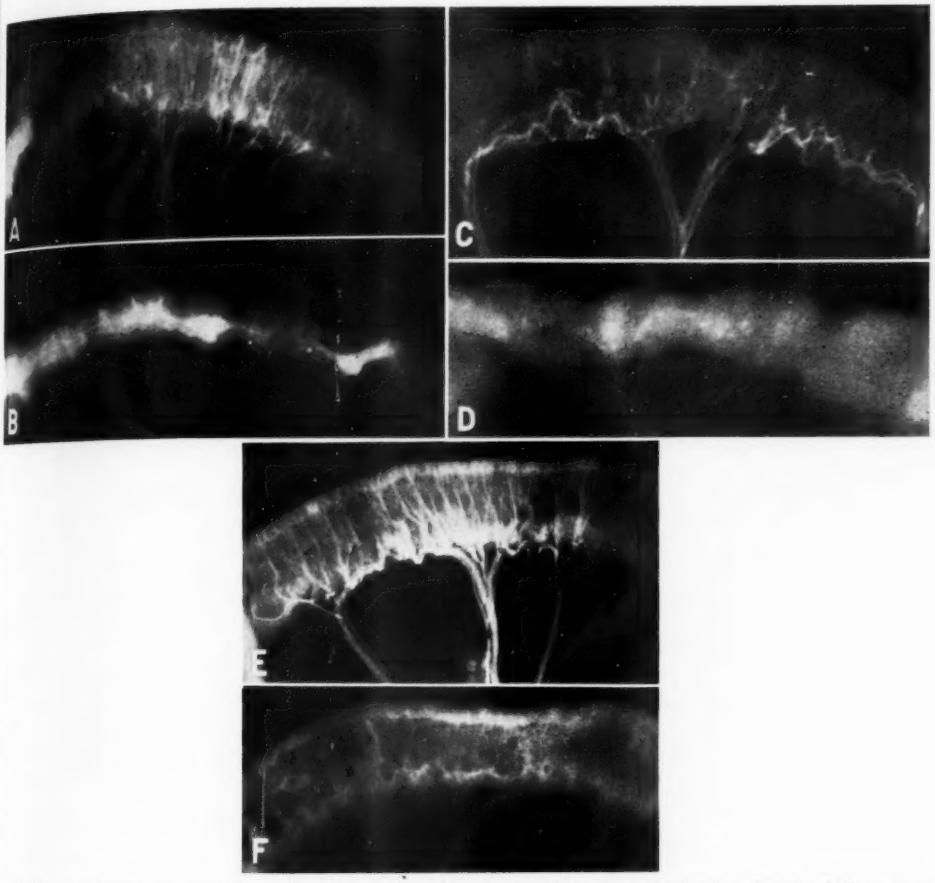

Fig. 3. A. Mesenteric arteriogram in a dog obtained immediately following the injection of 8 ml. of 50 per cent Miokon. B. Same loop of bowel three minutes following the injection. There is marked residual contraction of the bowel, some extravasation into its wall, and also leakage of contrast medium into the lumen. The dog survived and, following resection three weeks later, mucosal necrosis was demonstrated by histologic sections.

C. Mesenteric arteriogram obtained by injection of 8 ml. of 50 per cent Hypaque. Extravasation into the bowel wall is only minimal. D. Slight contraction of the bowel persists three minutes after the injection. Only minimal extravasation is evident. Three weeks following resection, histologic sections showed patchy necrosis of all layers of the bowel.

E and F. Mesenteric arteriogram and radiograph of the same bowel loop three minutes after the injection of 8 ml. of 60 per cent Renografin. The contraction of bowel is minimal, and there is slight extravasation of contrast material into its wall. Histologic sections following resection three weeks later failed to show any abnormality.

by loss of nuclear staining and homogenization of muscle fibers, was seen. This varied from patchy necrotic areas to complete necrosis of all muscle fibers (Figs. 1 and 2). When not generalized, the necrosis was more marked in the outer muscle layer. Almost no associated inflammatory reaction was noted. Vasculitis and other vessel changes were uncommon and of minor degree.

Ten of 17 (58.5 per cent) loops injected with Miokon showed muscle necrosis (Table I). In 8 loops (47.0 per cent) the necrosis was patchy in character. In 2 (11.8 per cent) complete necrosis with dissolution of the bowel wall occurred, and both animals died with peritonitis. Of the 7 loops with no muscle necrosis 3 showed complete necrosis of the mucosa. If these are included as abnormal, 13 of 17 (76.5 per cent) loops injected with Miokon demonstrated necrosis of either muscle or

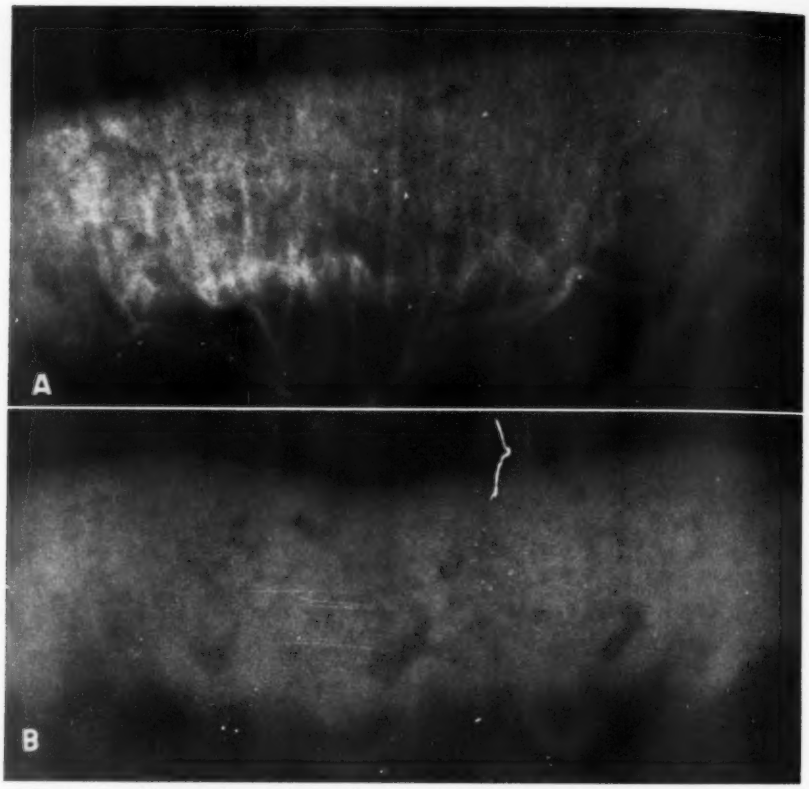

Fig. 4. A. Mesenteric arteriogram in a dog following injection of 2 ml. of 25 per cent Miokon. The arteriogram is of poor quality due to the small amount of the medium and its low concentration. B. No extravasation is demonstrated in the radiograph three minutes following the injection. Note the absence of residual contraction. Histologic sections nevertheless showed patchy necrosis in the outer muscular layer.

mucosa. No consistent decrease in the amount or incidence of muscle necrosis attended a decrease in the volume or concentration of Miokon. Muscle necrosis was observed even when only as little as 2 ml. of 25 per cent Miokon was injected (Fig. 4).

In 2 of 17 ileal loops (11.8 per cent) injected with Hypaque there was muscle necrosis, patchy in both cases (Table I). None of the Hypaque loops perforated and none of the animals died. The necrosis occurred only with the larger doses of the medium. If the loops injected with 16 ml. of Hypaque are excluded, 93 per cent were normal as compared to 41.2 per cent of those injected with the same amount of Miokon.

None of the 12 loops of ileum injected with Renografin showed necrosis, and none of the dogs died (Table I).

The length of each injected loop of ileum was measured on the roentgenogram, the mean length of all loops being 11.7 cm. The mean length of all loops with necrosis was 10.8 cm. The difference is not statistically significant.

Numerous loops were flushed with 20 ml. of saline immediately after the injection of Miokon, Hypaque, or Renografin. This flushing did not alter the incidence of muscle necrosis.

There was no correlation between the amount of extravasation of the contrast medium, contraction of the intestine, and the amount of necrosis. Neither dilatation nor constriction of vessels was observed.

TABLE I: RESULTS OF INJECTION OF MIOKON, HYPAQUE, AND RENOGRAFIN INTO ILEAL LOOPS

Amount and Concentration Injected	No. of Loops Injected	No. of Necrotic Loops and Grade of Necrosis (0 Through 2+)*		
		0	+	2+
Miokon				
8 c.c. 50%	5	3	0	2
4 c.c. 50%	4	2	2	0
2 c.c. 50%	2	0	2	0
4 c.c. 50%	3	1	2	0
2 c.c. 25%	3	1	2	0
TOTAL	17	7(41.2%)	8(47.0%)	2(11.8%)
Hypaque				
16 c.c. 50%	3	2	1	0
8 c.c. 50%	4	3	1	0
4 c.c. 50%	4	4	0	0
2 c.c. 50%	2	2	0	0
4 c.c. 25%	2	2	0	0
2 c.c. 25%	2	2	0	0
TOTAL	17	15(88.2%)	2(11.8%)	0
Renografin				
16 c.c. 60%	2	2	0	0
8 c.c. 60%	2	2	0	0
4 c.c. 60%	2	2	0	0
2 c.c. 60%	2	2	0	0
4 c.c. 0%	2	2	0	0
2 c.c. 30%	2	2	0	0
TOTAL	12	12(100%)	0	0

*0 = no necrosis. + = patchy necrosis without perforation. 2+ = complete necrosis with perforation.

DISCUSSION

This study is a comparison of the effects of intra-arterial Miokon, Hypaque, and Renografin upon the small intestine of the dog. It has been assumed that no ill effects attend the intra-arterial injection of these radiopaque media. This study and others suggest that permanent tissue damage may follow such procedures. When injected into the mesenteric arteries of the small intestine, Renografin appears to be the safest and Miokon the most dangerous.

The method described in this report can be used as a test to determine tissue toxicity of intravascular contrast media.

SUMMARY

For a comparative study, in dogs, of the effects in the small intestine of intra-arterial injections of contrast media, 56 loops of ileum were dissected free and cannulated with a 21-gauge scalp-vein needle. In 10 control loops either injections of 20 ml. of normal saline were made or the artery was ligated and nothing was injected. Seventeen loops were injected with Miokon, 17 with Hypaque, and 12 with Renografin. Small-bowel muscle necrosis attended 58.5 per cent of the Miokon injections and 11.8 per cent of the Hypaque injections. In no loop injected with Renografin did muscle necrosis occur.

This study suggests that of the three media tested, Renografin is the safest and Miokon the least safe.

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REFERENCES

1. CHAPLIN, H., JR., AND CARLSSON, E.: Changes in Human Red Cells During in Vitro Exposure to Several X-Ray Contrast Media. Am. J. Roentgenol. In press.

2. CICCANTELLI, M. J., GALLAGHER, W. B., SKEMP, F. C., AND DIETZ, P. C.: Fatal Nephropathy and Adrenal Necrosis after Translumbar Aortography. New England J. Med. **258:** 433–435, Feb. 27, 1958.

3. FISCHER, H. W., AND ECKSTEIN, J. W.: Comparison of Cerebral Angiographic Contrast Media by Their Circulatory Effects. An Experimental Study. Am. J. Roentgenol. **86:** 166–177, July 1961.

4. HOPPE, J. O.: Some Pharmacological Aspects of Radiopaque Compounds. Ann. New York Acad. Sc. **78:** 727–739, July 2, 1959.

5. LANCE, E. M., AND KILLEN, D. A.: Experimental Appraisal of the Agents Employed as Angiocardiographic and Aortographic Contrast Media. I. Neurotoxicity. Surgery **46:** 1107–1117, December 1959.

6. LLOYD, F. A., AND COTTRELL, T. L.: Diatrizoate Sodium. Ann. New York Acad. Sc. **78:** 987–992, July 2, 1959.

7. MARGULIS, A. R., HEINBECKER, P., AND BERNARD, H. R.: Operative Mesenteric Arteriography in the Search for the Site of Bleeding in Unexplained Gastrointestinal Hemorrhage (Preliminary Report). Surgery **48:** 534–539, September 1960.

8. MARGULIS, A. R., AND HEINBECKER, P.: Mesenteric Arteriography. Am. J. Roentgenol. **86:** 103–113, July 1961.

9. MCAFEE, J. G.: A Survey of Complications of Abdominal Aortography. Radiology **68:** 825–838, June 1957.

10. MELICK, W. F., BYRNE, J. E., AND BOLER, T. D.: The Experimental and Clinical Investigation of Various Media Used in Translumbar Aortography. J. Urol. **67:** 1019–1025, June 1952.

11. ÖDMAN, P.: Percutaneous Selective Angiography of the Superior Mesenteric Artery. Acta radiol. **51:** 25–32, January 1959.

12. SCHOBINGER, R., BLACKMAN, G., AND LIN, R. K.: Operative Intestinal Arteriography. Acta radiol. **48:** 330–336, November 1957.

13. STOKES, J. M., AND BERNARD, H. R.: Nephrotoxicity of Iodinated Contrast Media: Quantitative Effects of High Concentration upon Glomerular and Tubular Functions. Ann. Surg. **153:** 299–309, February 1961.

14. WALLINGFORD, V. H.: General Aspects of Contrast Media Research. Ann. New York Acad. Sc. **78:** 707–719, July 2, 1959.

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SUMMARIO IN INTERLINGUA

Le Effectos del Injection Intra-Arterial de Miokon, Hypaque, e Renografin in le Intestino Tenue del Can

Pro un studio comparative del effectos de injectiones intra-arterial de substantias de contrasto ad in le intestino tenue, 56 ansas del ileum de canes esseva liberate per dissection e cannulate con un agulia cave de calibre 21. In 10 ansas de controlo un de duo manovras esseva effectuate: injectiones de 20 ml de solution salin normal esseva facite o le arteria esseva ligate e nulle injection esseva facite. Dece-septe ansas recipeva injectiones de Miokon, 17 de Hypaque, e 12 de Renografin. Necrosis de musculo del intestino tenue occurreva in association con 58,5 pro cento del injectiones de Miokon e 11,8 pro cento del injectiones de Hypaque. Nulle necrosis muscular occurreva in ulle del casos a injection de Renografin.

Iste studio suggere que inter le tres substantias de contrasto testate, Renografin es le plus innocente e Miokon le minus innocente.

Treatment of Cancer of the Anus[1]

T. A. WATSON, M.B., Ch.B., D.M.R.[2]

THERE IS A widespread impression that the best results in the treatment of cancer of the anus are obtained by radical surgery, and that radiation has little or no place in the management of this disease. It is the object of this paper to show that, in many cases, radiotherapy is the treatment of choice and that permanent cure, with preservation of the anal sphincter and absence of complications, frequently follows.

Cancer of the anus, usually epidermoid in type, is not common. From 1947 to 1954 only 9 new cases were encountered in the Saskatoon Cancer Clinic, representing 4 per cent of 239 new cases of cancer of the rectum seen in that period. This percentage is in accordance with the comparative figures found in large series (4, 6, 8, 16).

Most authors advise radical surgery in all types of anal cancer, *i. e.*, abdominoperineal excision (1, 3, 4, 7–10). A few recommend radiation therapy in certain cases (2, 12, 13). Some prefer local excision, usually for small lesions of the anal margin (5, 10, 11). It is generally agreed that the only treatment for involved lymph nodes is surgery.

It is useful to classify these tumours according to their site of origin. The first type arises below the dentate line and extends into the peri-anal skin; the second arises in the anal canal, extending up and down; the third, quite rare, infiltrates upward into the rectum and is usually called anorectal cancer. It is also epidermoid in nature.

The spread in cancers of the anus of the first type is to the inguinal lymph nodes. Block dissection on the involved side should be carried out only when it is known that secondary involvement has taken place. Though this procedure is often unsuccessful, it is the treatment of choice. It is seldom, if ever, successful when both inguinal regions are involved. Stearns (15) has shown that prophylactic block dissection has no place. Judd and DeTar (7), with commendable candour, arrive at the following conclusions: " . . . when the nodes were not involved, bilateral dissections were attended by relatively good results. However, when the nodes were involved, none of the patients survived five years, no matter how radical the approach." The use of local radiation treatment in cancer of the lower anus, therefore, can hardly be claimed to jeopardize the subsequent course, with respect to lymph-node metastases, since the decision as to the performance of block dissection of the groins is in no way affected.

The lymphatic spread from cancer of the anal canal is frequently upward to the pararectal, superior rectal, and inferior mesenteric nodes. It must be admitted that only by abdominoperineal resection can the primary tumour and the lymphatic spread be adequately dealt with. In spite of this, some of these cases can be successfully treated with radium implantation.

The treatment of the third type—anorectal carcinoma—is admittedly surgical, both because of the internal lymphatic spread and because of the inaccessibility of the primary tumour to radium.

Results of surgical treatment vary, as far as five-year survivals are concerned, from 30 to 52 per cent (4, 5, 7, 8, 11), depending to some extent on the type of calculation employed. Bond (2), in his series, compares a five-year survival rate of 48 per cent for those treated with surgery alone, to 43 per cent for those treated by radium implantation. He considers the latter indicated in cancers of the anus and anal canal involving less than half the circum-

[1]Presented at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960.

[2]Saskatoon, Sask., Canada.

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Fig. 1. Anteroposterior and lateral radiographs (Case 13128). Separation of planes 2.3 cm. Average area of planes 20 sq. cm.

ference and less than 1.0 cm. thick. Paterson (14) reports a 53 per cent crude five-year survival rate in a series of 19 cases treated by radium implantation.

Of the 9 patients with cancer of the anus admitted to the Saskatoon Cancer Clinic between 1947 and 1954, 2 were suffering from recurrent or residual disease, having been previously treated elsewhere. One patient had had a basal-cell carcinoma of the anal margin removed locally immediately before admittance. This patient remains well, without further treatment, nine years later. The remaining 6 patients, all with carcinoma of the anal margin or anal canal, were treated by radium implantation. Four of them remain well eight to ten years after treatment. One died of coronary occlusion four years and ten months after treatment, with no evidence of residual, recurrent, or metastatic tumour at death. In only 1 patient, eighty-four years old, secondary nodes developed in the groin four months after radium therapy, and a block dissection was performed. The nodes subsequently recurred and were treated by radium implantation, the anus became fissured and ulcerated, and a colostomy was performed eighteen months after the original treatment. Postmortem no residual tumour was found in the anus, groins, or elsewhere, death being due to senility, arteriosclerosis, and mesenteric embolism. This was the only patient to have a painful anus following radium treatment. All the others had comfortable and normally functioning ani. One, who is now well, had a local recurrence at the anus eight and one-half years after treatment, and a successful abdominoperineal resection was performed.

It will thus be seen, in this small consecutive series, that radium implantation has produced excellent curative results, with a normal anus in 5 out of 6 patients. It must be admitted that we have been fortunate in seeing early cases, and in only one did metastasis to the groin occur. The size of tumours varied from 5 × 4.5 cm. to 1.3 × 1 cm.

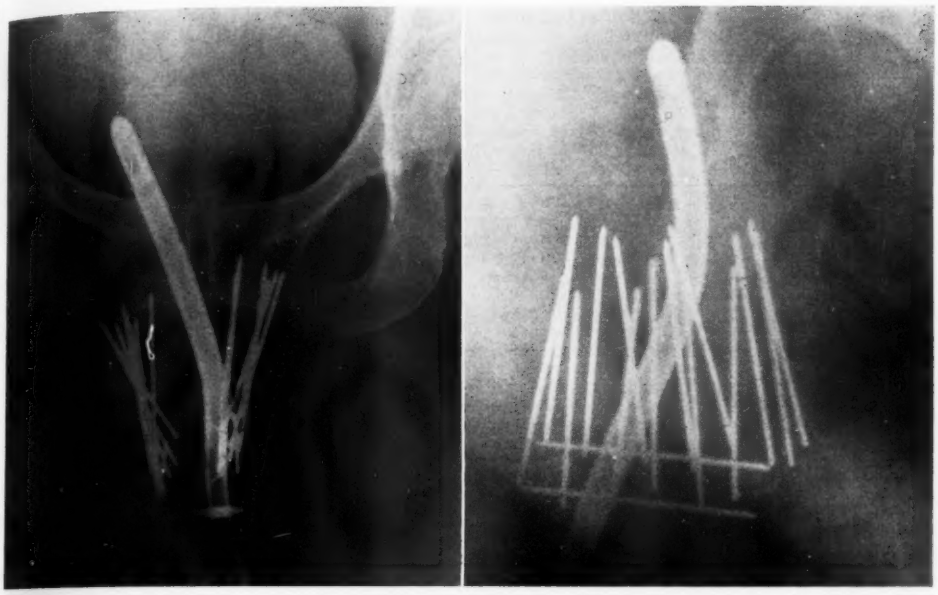

Fig. 2. Anteroposterior and lateral radiographs (Case 11537). Separation of planes 3 cm. Average area of planes 27 sq. cm.

TECHNIC

The most satisfactory geometrical pattern for radium implantation at the anus is the two-plane implant. The tumour should not be larger than will be adequately covered by such an implant, and the separation of the planes should not be more than 3 cm. Occasionally a volume implant may be indicated, but radium treatment of large irregular areas is generally contraindicated. All 6 cases reported here were suitable for two-plane implantation. Single-plane implants are usually not indicated because of the tendency of the growth to curve around, or encircle, the circumference of the anus.

The patient is given a general anaesthetic and placed in the lithotomy position. With the index finger of the left hand in the anus, radium needles are thrust upward through the skin of the buttock, starting below the lesion, their course being kept as medial as possible under guidance by the finger in the rectum. Care is taken not to perforate the rectal mucosa. To outline the urethra, a rubber catheter may be inserted into the bladder and removed when the implant is complete. The planes are sagittal and each extends in front of and behind the anus a sufficient distance to allow a margin at the edge of the tumour. Usually needles of an overall length of 5.7 cm. with an active length of 4.5 cm. are used, the strength of the peripheral needles being 3 mg. and the interior needles 1.5 mg. Needles in each plane should be separated by a little more than 1 cm. The upper ends of the planes are necessarily uncrossed, but some discretion should be used as to the crossing of the lower ends. If the lower ends are quite near the anal margin, then it probably is wisest to "cross" with half-strength rather than full-strength needles.

After insertion, all needles are threaded with thin German silver wire. The projecting ends of the needles are then sunk under the skin surface and are retained in place by two silk sutures on each side. Anteroposterior and lateral roentgenograms of the implant are taken, a twenty-five cent piece being placed just below the implant so that magnification can be accurately calculated. It is not difficult to in-

TABLE I: CARCINOMA OF THE ANUS: TECHNICAL DETAILS
(All two-plane radium implants)

Case No.	Separation of Planes (cm.)	Average Area of Planes (sq. cm.)	Dose at 0.5 cm. from Plane (r)	Time (hours)	Results
6,793	1.25	8	6000	118	Died 4 yr., 10 mo. Coronary occlusion. No recurrence
9,706	1.7	16	4500	79	Well 10 yr.
11,537	3.0	27	5000	117	Well 10 yr.
11,972	2.3	16	5750	129	Well 10 yr.
13,128	2.3	20	6000	129	Recurred 8½ yr.
14,086	2.0	45	6000	162	Died 2½ yr. Necrosis. No residual tumour

sert the needles parallel to one another, nor to assure a reasonably small separation of planes.

An attempt is usually made to keep the bowels from moving until the radium is removed, but this is not always successful and is not absolutely necessary. Tincture opii, minims 10 q.i.d., and a low residue diet will usually prevent bowel movements for several days.

Dosage calculations are made according to the Paterson-Parker system. The dose at 0.5 cm. from either plane in the cases presented varied from 4,500 r in seventy-nine hours to 6,000 r in one hundred and sixty-two hours. The separation varied from 1.25 to 3 cm. The dose finally decided upon in each case was governed by the size of the planes, separation, and the dosage rate as calculated from the placement films. The various technical factors on all patients are listed in Table I, and examples of placement films are given in Figures 1 and 2.

REACTIONS

No serious reactions were observed in any of the patients, except the one who eventually had to have a colostomy because of pain and spasm of the anus. Moderate moist reactions, which did not require hospitalization and caused no severe discomfort, occurred in the other 5. Aureomycin or neomycin ointment was prescribed. All patients responded to medication within three to five weeks and experienced no trouble thereafter.

DISCUSSION

Since cancer of the anus is epidermoid in type and accessible, it should be eminently amenable to radiation treatment by analogy with accessible epidermoid carcinoma elsewhere. The difficulty is that radiation reactions in this site are apt to be severe because of the moistness of the part, frequent irritation, and constant movement. For these reasons high-dose irradiation must be confined to as small a volume as possible, and the skin particularly should be irradiated over a minimum area. External irradiation is, therefore, contraindicated, and if curative radiation treatment is contemplated, interstitial radium is the obvious choice.

It has been shown that, in lesions that are not extensive, two-plane radium implants can be very satisfactory, from the point of view both of cure and of preservation of a normally functioning anus. This is accomplished without serious reactions. A plea is made for consideration of this treatment in preference to mutilating radical surgical procedures, which necessitate colostomy. Lymphatic spread is not common in early lesions. When it does occur, however, it is usually to the inguinal nodes, where block dissection is not prejudiced by radium treatment to the primary tumour.

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REFERENCES

1. BACON, H. E., VENTURA, R., AND SAUER: Epidermoid Carcinoma of Canal; Report of 28 Cases. J. Mt. Sinai Hosp. **17:** 478–485, March-April 1951.
2. BOND, W. H.: [In] Discussion on Squamous Cell Carcinoma of the Anus and Anal Canal. Proc. Roy. Soc. Med. **53:** 411, June 1960.
3. BUXTON, R. W.: Squamous Cell Anal Carcinoma. Arch. Surg. **67:** 821–838, December 1953.
4. GABRIEL, W. B.: Squamous-cell Carcinoma of Anus and Anal Canal; Analysis of 55 Cases. Proc. Roy. Soc. Med. **34:** 139–157, January 1941.
5. GABRIEL, W. B.: [In] Discussion on Squamous Cell Carcinoma of the Anus and Anal Canal. Proc. Roy. Soc. Med. **53:** 403, June 1960.
6. GRIFFIN, O. P.: Epidermoid Carcinoma of Anus and Rectum. Am. J. Surg. **88:** 707–709, November 1954.

7. JUDD, E. S., JR., AND DETAR, B. E., JR.: Squamous-cell Carcinoma of Anus; Results of Treatment. Surgery **37**: 220–228, February 1955.
8. GRINNELL, R. S.: Analysis of 49 Cases of Squamous Cell Carcinoma of Anus. Surg., Gynec. & Obst. **98**: 29–39, January 1954.
9. MCQUARRIE, H. B., AND BUIE, L. A.: Epithelioma of Anus. Postgrad. Med. **7**: 402–409, June 1950.
10. MILLAR, T. M.: [In] Discussion of Squamous Cell Carcinoma of the Anus and Anal Canal. Proc. Roy. Soc. Med. **53**: 410, June 1960.
11. MORSON, B. C.: [In] Discussion of Squamous Cell Carcinoma of the Anus and Anal Canal. Proc. Roy. Soc. Med. **53**: 416, June 1960.
12. MURPHY, W. T.: Radiation Therapy. Philadelphia, Penna., W. B. Saunders Co., 1959.
13. PATERSON, R.: The Treatment of Malignant Disease by Radium and X-rays. Baltimore, Md., Williams & Wilkins Co., 1948.
14. PATERSON, R., TOD, M., AND RUSSELL, M.: The Results of Radium and X-ray Therapy in Malignant Disease; Being the Third Statistical Report from the Radium Institute, the Christie Hospital, and Holt Radium Institute, Manchester, England, Years 1940–1944 Inclusive Assessed at 5 Years and 1934–1938 Assessed at 10 Years. Baltimore, Md., Williams & Wilkins Co., 1950.
15. STEARNS, M. W., JR.: Epidermoid Carcinoma of Anal Region; Inguinal Metastases. Am. J. Surg. **90**: 727–733, November 1955.
16. SWEET, R. H.: Results of Treatment of Epidermoid Carcinoma of Anus and Rectus. Surg., Gynec. & Obst. **84**: 967–972, May 1947.

SUMMARIO IN INTERLINGUA

Tractamento de Cancere del Ano

Es reportate un micre serie consecutive de casos de carcinoma anal tractate per implantation de radium. Le casos esseva relativemente non-avantiate. Nulle de illos monstrava infiltration usque ad in le recto. Quatro de 6 patientes remaneva ben-portante inter octo e dece annos post le tractamento. Un moriva ab altere causas quatro annos e dece menses post le tractamento, sin signos de cancere residue, recurrente, o metastatic. In solmente 1, metastase al nodos inguinal se disveloppava quatro menses post le implantation de radium. In iste caso, dissection in bloco esseva requirite. Le nodos recurreva subsequentemente e esseva tractate per radium. Le ano deveniva fissurate e ulcerate, e colostomia esseva requirite. Al necropsia, nulle tumor esseva trovate in le ano, le inguines, o alterubi.

Omne le 6 casos in iste serie esseva tractate per un implantation biplanar de radium. Usualmente agulias de un longor total de 5,7 cm con un longor active de 4,5 cm esseva usate. Le dose a un distantia de 0,5 cm ab le un e le altere plano variava inter 4.500 r in septanta-novem horas e 6.000 r in cento sexanta-duo horas. Le separation variava inter 1,25 e 3,0 cm. Con le sol exception notate in supra, nulle significative reactiones adverse esseva provocate per le tractamento. Dissection de bloco inguinal non es prejudiciate per therapia a radium in le tumor primari.

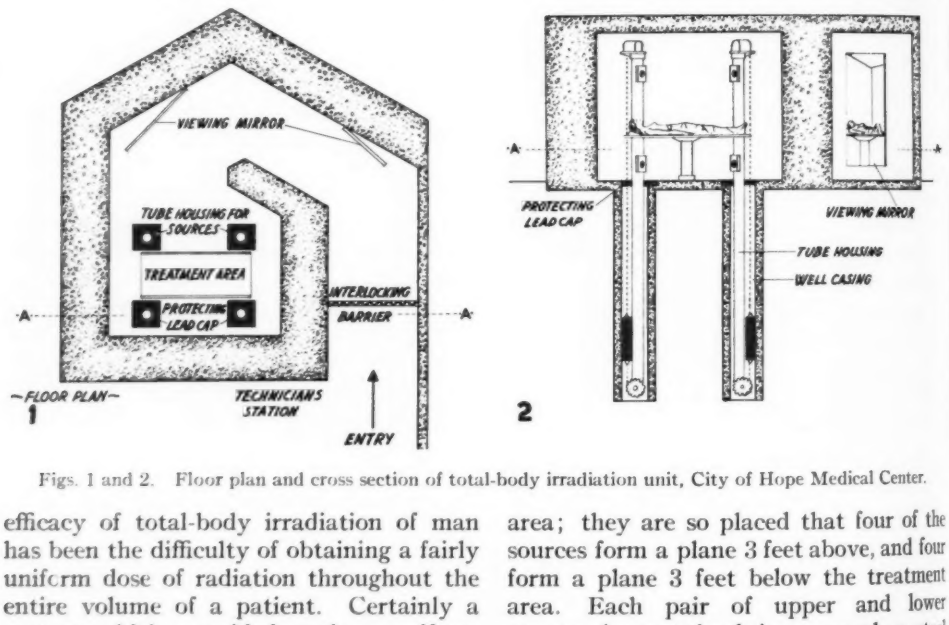
Dosimetry for a Total-Body Irradiation Chamber[1]

MELVILLE L. JACOBS, M.D., and LEON PAPE, M.Sc.

IN THE PAST few years there has been a rapidly growing interest in the problems of radiation protection in cases of exposure of large areas of the human body. In addition, much work has been done in the field of organ transplants, particularly with respect to the management of leukemia with bone-marrow transplants.

It is of interest to note that more success has attended the studies on experimental animals than on man. It is postulated that one of the problems in evaluating the efficacy of total-body irradiation of man has been the difficulty of obtaining a fairly uniform dose of radiation throughout the entire volume of a patient. Certainly a system which provided such a uniform energy deposition would eliminate a variable in the ultimate evaluation of total-body irradiation. It is the object of this paper to describe a physical system designed and constructed with this in view and to report the initial results of the dosimetry connected with it, as well as the problems encountered.

The irradiation chamber measures approximately 11 × 11 feet. In its center is a treatment area defined by four upright posts (Fig. 1), which is approximately 2 feet wide and 6 feet long, representing a horizontal plane 3 feet above the floor of the treatment chamber. The radiation is produced by eight cesium sources with an initial strength of 300 curies each. When in treatment position, the sources are housed in the four upright posts and are located in the corners of the treatment area; they are so placed that four of the sources form a plane 3 feet above, and four form a plane 3 feet below the treatment area. Each pair of upper and lower sources is contained in a seamless steel tube which, in turn, is mounted in a steel well casing (Fig. 2).



Figs. 1 and 2. Floor plan and cross section of total-body irradiation unit, City of Hope Medical Center.

The four casings are sunk to a depth of 12 feet in the ground below the chamber and are encased in concrete jackets. The source tubes rise to a point 7 feet above the chamber floor. Each tube supports an independent chain-drive mechanism which

[1] From the City of Hope Medical Center (M. L. J., Chairman of the Department of Radiology; L. P., Chief Physicist), Duarte, Calif. Presented at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960.

is used to bring the sources from "safe" position in the underground wells to "treatment" position. Each set of sources can be positioned independently or all four sets can be positioned for treatment simultaneously. The counterweights are adjusted so as to provide for source return to "safe" position in case of power failure. The sources are housed in standard international treatment capsules which, in turn, are mounted in carrier capsules. The carrier capsules for each set are connected through a rigid steel bar which maintains a fixed separation of 6 feet between sources. Movement and positioning of each pair of sources are therefore simultaneous.

Each treatment portal has a removable beam-absorber holder to which a wide variety of absorbers and beam-shaping blocks can be secured.

Finally, the control panel contains a row of lights for each column. These are activated by microswitches and indicate source position in each column during movement.

In respect to the program of dosimetry, the problem of a suitable phantom was resolved by the fabrication of a full-size mannequin constructed of Fiberglas, a full-body plaster-of-Paris cast of a male employee being used as a mold. In the final construction stages, Lucite tubes were inserted at suitable intervals to provide channels for the dosimeters throughout the extent of the phantom. Phantom-shell thickness is approximately 1 mm. and a filler of rice is employed to simulate tissue (Fig. 3).

Measurements were carried out with a Victoreen condenser-r meter and multiple small Landsverk thimble chambers. These units were calibrated at their respective factories for energy dependence.

An initial dose distribution was determined in air (Fig. 4). This was at first disappointing because, while the variation in the width of the treatment field was 15 per cent, in the long dimension the dose rate was 50 per cent of the central dose rate. Upon reflection, however, this did not seem to be as unfortunate as it first appeared, since the body volume follows the same variation, namely, greatest in the midportion and decreasing at either end. The effect of a body in the field, then, would tend to even out the variation.

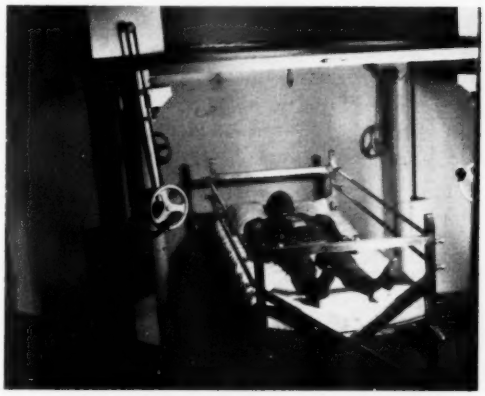


Fig. 3. Total-body irradiation unit; Fiberglas phantom.

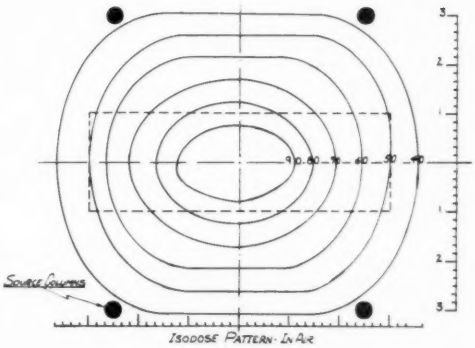
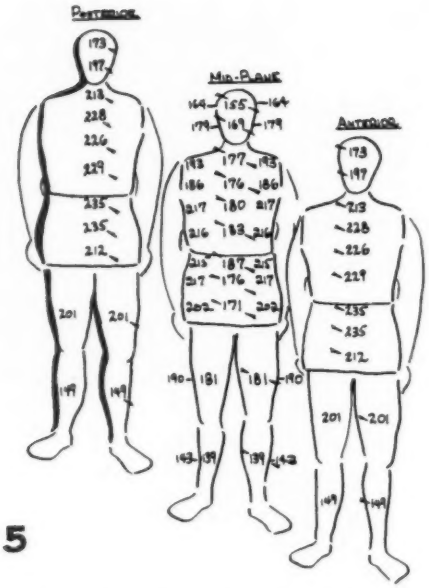


Fig. 4. Isodose pattern in air.

Figure 5 shows the point-dose distribution in the phantom with no beam absorbers. Here the maximum variation from the central dose rate is only 26 per cent. The point-dose distribution in the phantom with a 1/8-inch lead beam absorber in position is shown in Figure 6; here the maximum variation is only slightly better, namely, 22 per cent. If, however, a central absorber is added to move the central dose toward the peripheral dose, we find a sharp improvement.

Figure 7 gives the dose distribution for a 1/4-inch lead plate plus a convex circular central beam absorber 1/4-inch thick.



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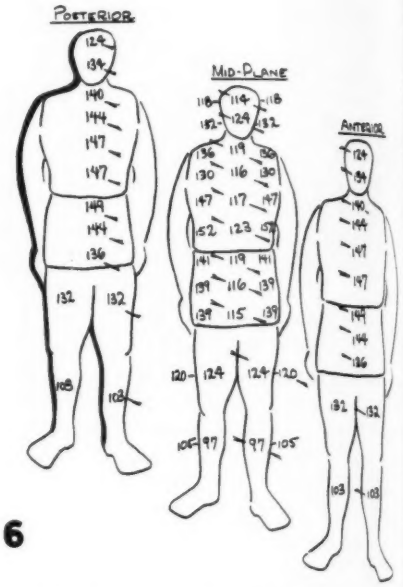

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Fig. 5. Filtration, none; readings in r per hour; output in air, 280 r per hour. Average midplane-midbody dose rate, 193 r an hour.

Fig. 6. Filtration, 1/8-inch lead plate; readings in r per hour. Average midplane-midbody dose rate, 131 r an hour.

Here the variation from central to peripheral dose is only ~9 per cent.

At this point it is worthwhile considering the variations off the central axis. Obviously these are larger than the variations along the long axis. As seen in Figure 7, the average variation from central to lateral aspect in the midbody is approximately 17 per cent. To investigate this, a series of isodose patterns were made with use of the central volume as representative. A Presdwood cross section was fabricated to fit in the midsection of the phantom. Multiple chamber holes in this Presdwood section made possible a series of point measurements.

Figure 8 represents the isodose pattern for a 1/8-inch lead beam absorber. In developing the pattern, the average dose rate was used as the 100 per cent base line. It is apparent that, within the greatest portion of the volume, the variation is ±8 per cent. This is consistent with the point-dose measurements in the total phantom. Figure 9 is the isodose

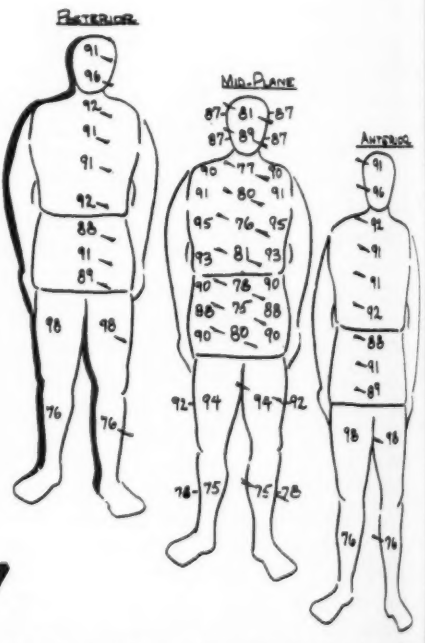

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Fig. 7. Filtration, 1/4-inch lead plate plus conver circular disk; output in air is 136 r per hour. Average midplane-midbody dose rate, 85 r per hour.

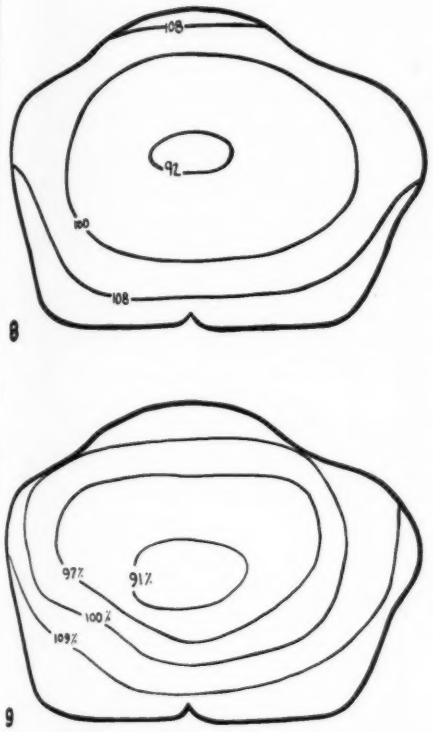

Fig. 8. Total-body irradiation chamber. Isodose pattern measured in Presdwood phantom. Filtration 1/8-inch lead plate; average dose rate 131 r per hour.
Fig. 9. Isodose pattern measured in Presdwood phantom. Filtration, 1/4-inch lead plate.

pattern with a 1/4-inch lead plate and is similar to Figure 8.

While these initial dosimetry studies have indicated the degree of field uniformity obtainable, significant studies are still to be made. For instance, a prime question is that of integral dose. In ordinary therapy, the concept of integral dose is invoked as a limiting condition, the best field being that which will give the greatest tumor dose with the least integral dose. In total-body irradiation, the organ dose and, therefore, the integral dose in a given volume must be considered as a desirable indicator of dose rather than point dose. In this respect, different systems of dosimetry must be considered—photographic, chemical, and biological.

Correlation between integral dose and biological response must be investigated, as well as problems of energy distribution, scattering, and automatic dose-plotting systems. These projects are being set up in our program prospectus.

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REFERENCES

JACOBS, M. L., AND PAPE, L.: A Total Body Irradiation Chamber and Its Uses. J. Appl. Radiation & Isotopes **8:** 141–143, July 1960.

THOMAS, E. D., LOCHTE, H. L., JR., AND FERREBEE, J. W.: Irradiation of the Entire Body and Marrow Transplantation: Some Observations and Comments. Blood **14:** 1–23, January 1959.

BRUCER, M.: Description of Oak Ridge Total Body Irradiation Facility, Oak Ridge Institute of Nuclear Studies. Personal correspondence 1960.

KING, E. R.: Description of the Navy Total Body Irradiation Unit at U. S. Naval Hospital, Bethesda, Md. Personal correspondence, 1960.

DISCUSSION

Bernard Roswit, M.D. (Bronx, N. Y.): There seems to be no end to the versatility of these tiny dosimeters. We used human cadavers and trocars to introduce plastic tubing carrying multiple microdosimeters. We have placed them nearly everywhere in the body. We have gone to the living patient to put the catheters with dosimeters into the aorta, the heart, the bronchi, the brain, the kidney, and eventually into almost every body tissue and space. We hope to correlate these results some day with Mr. Pape's.

John S. Laughlin, Ph.D. (New York, N. Y.): I noticed that 85 r per hour was mentioned as the average midplane dose. I wonder how long the patient is exposed to this dose.

Mr. Pape: The program has just started. As far as patient exposure is concerned, we are using a total-body exposure of 300 r in order to get a feel of patient management and response. (This, however, is out of my province.) For a dose rate of 85 r per hour, the patient stays in the chamber about three and a half hours. During this time we make no restrictions on his motion within the bed and, if necessary, we will stop the treatment in order to allow him to relax or take care of any needs.

Dr. Laughlin: There is no other way of varying the dose rate?

Mr. Pape (*closing*): No, there isn't. The only way of varying dose rate is by filtration. Without filtration, we have midplane dose rates of the order of 193 r per hour.

SUMMARIO IN INTERLINGUA

Dosimetria pro un Camera de Irradiation del Corpore Total

Un del problemas in le evalutation del efficacia de un irradiation del corpore total de patientes human es le difficultate de obtener un satisfacentemente uniforme dose de radiation in omne partes del volumine integre del subjecto. In le presente communication, un systema physic es describite le qual esseva planate pro provider un uniforme deposition de energia. Le resultatos initial del dosimetria concernente iste systema es reportate, insimul con le problemas incontrate. Le radiation es producite per 8 fontes a cesium con un fortia initial de 300 curies per fonte individual. Quando illos es in position pro le tractamento, le fontes es includite in quatro pilares erecte in le quatro angulos del area de tractamento. Quatro del fontes forma un plano 3 pedes supra e 4 un plano 3 pedes infra le area de tractamento. Le phantoma es un mannequin de dimensiones normal construite ex Fiberglas con tubos de Lucite que es inserite a intervallos appropriate pro fornir canales pro dosimetros in omne partes del phantoma.

Studios dosimetric initial indica le grado de uniformitate de campo que pote esser obtenite, sed studios significative remane a completar, specialmente con respecto al dose integrai.

The Use of Radioactive Phosphorus in the Diagnosis of Thyroid Cancer[1]

NORMAN B. ACKERMAN, M.D.,[2] and JAMES F. MARVIN, Ph.D.

APPROXIMATELY twenty years ago it was first demonstrated that radioactive phosphorus (P^{32}) uptake is selectively increased in malignant tissue (6, 11). During the past two decades P^{32} has been used to study numerous experimental and human tumors. Since thyroid cancer is often difficult to diagnose clinically, occasionally presenting a problem even to the pathologist examining microscopic sections, attention has been turned toward the diagnostic use of P^{32} uptake, particularly in solitary nodular and multinodular goiters.

METHOD

The P^{32}-uptake test has been performed on a total of 61 patients with solitary nodular and multinodular goiters. These patients, including 47 women and 14 men, seventeen to seventy-seven years of age, were from the out-patient and in-patient services of the University of Minnesota Hospitals. They were given an oral dose of 500 microcuries of P^{32} in the form of sodium phosphate and were tested for uptake twenty-four hours later. With an eye-probe Geiger-Müller tube (Anton Laboratories Model 222), multiple counts were recorded over the thyroid nodule and over surrounding areas. Adjacent thyroid and anterior neck tissue served as a control to the suspicious nodule. During this study background counts averaged 10 cpm and counts over normal tissue averaged 110 cpm. The ratio of P^{32} uptake over the suspected tissue as compared with the normal tissue was calculated. An increase of P^{32} uptake over the nodule of 20 per cent or more was considered a positive test.

In most instances the P^{32}-uptake test was performed prior to any I^{131}-uptake studies. Since P^{32} is purely a beta-particle emitter, I^{131} studies can be carried out successfully immediately following its use. When I^{131} was administered first, it was necessary to delay the P^{32} test for at least three weeks, until residual iodine radioactivity had decreased to a minimum. Any remaining radioactivity was treated as part of background and was subtracted from total Geiger-Müller tube radioactivity.

RESULTS

In 7 of the 61 patients tested, the P^{32} uptake over the nodule was increased by 20 per cent or more, which was considered a positive test for cancer. The range of increase was from 23 to 61 per cent. In the remaining 54 patients the test was negative, with increases of P^{32} uptake of 12 per cent or less (12 to minus 22 per cent), except for 1 case with a 16 per cent increase.

Of the group of 54 patients with negative tests, 32 were subsequently operated upon and tissue diagnoses were obtained (Table I). On microscopic section almost all the lesions proved to be benign adenomas. Three patients had hyperthyroid nodules and 1 had a thyroglossal duct cyst. Calcified, cystic, or fibrotic nodules were present in several patients in whom a markedly decreased avidity for P^{32} over the nodules was demonstrated.

TABLE I: NEGATIVE P^{32} TESTS: OPERATIVE CASES

Patients	32
Ages	17–73 yr.
Sex	26 F; 6 M
P^{32} uptake (nodule/normal)	
Mean	0.96
Range	0.78–1.16
Microdiagnosis	
Benign	30 cases
Well differentiated follicular carcinoma	1 case
Carcinoma with fibrous tissue infiltration	1 case

[1] From the Departments of Surgery and Radiology, University of Minnesota Hospitals, Minneapolis, Minn. Accepted for publication in April 1961.

[2] Fellow under the auspices of the National Cancer Institute.

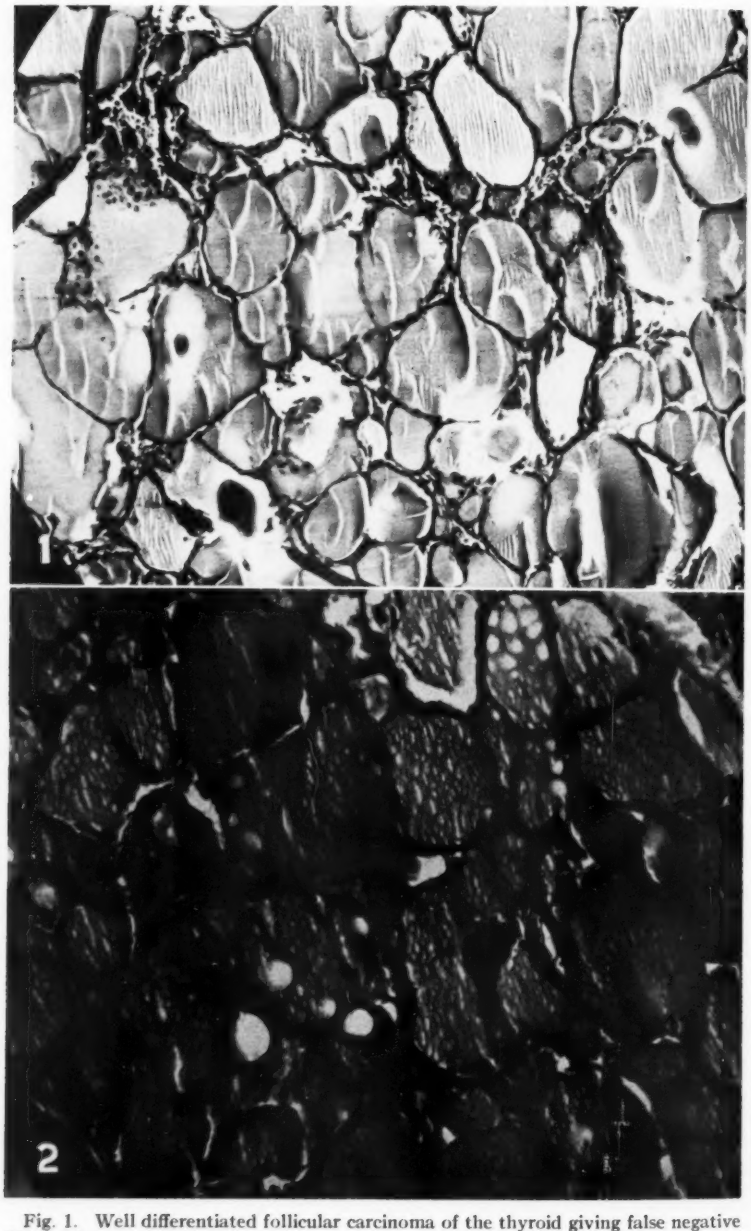

Fig. 1. Well differentiated follicular carcinoma of the thyroid giving false negative P^{32}-uptake test. ×135
Fig. 2. Well differentiated follicular carcinoma in discrete nodule of neck. ×210

Two false negatives were obtained: in 1 patient the thyroid gland appeared to consist of benign tissue (Fig. 1), but several small discrete nodules were noted in the midline of the neck, which appeared microscopically to consist of normal thyroid tissue (Fig. 2). There was no evidence of lymphoid tissue in these nodules, and re-examination of the thyroid gland tissue failed to reveal a focus of malignancy.

In view of the presence of possible neck metastases, however, the thyroid tissue was called an exceptionally well differentiated follicular carcinoma. The other false negative was obtained in a patient with a poorly differentiated follicular carcinoma with marked fibrous tissue infiltration (Fig. 3). In view of the low rate of phosphorus metabolism in fibrous tissue, it was not unexpected that lesions of this type might be difficult to detect.

Twenty-two patients with negative P^{32}-uptake tests were not operated upon for various reasons (Table II). The thyroid glands of all these patients were considered probably benign by clinical and laboratory evaluation. Eight patients in this group had, in addition to a thyroid nodule, other conditions of a more serious nature, including severe coronary heart disease, liver abscess, carcinoma of the colon, a recent cerebral hemorrhage, chronic renal insufficiency, etc. The risk of the thyroid surgery was felt to be unnecessary in view of the small chance of finding cancer. The other 14 patients were not advised to undergo surgery because of the attending physicians' opinions that the lesions were benign.

TABLE III: POSITIVE P^{32} TESTS

Patients	7
Ages	30–73
Sex	4 F; 3 M
P^{32} uptake (nodule/normal)	
Mean	1.37
Range	1.23–1.61
Microdiagnosis	
Malignant lesions	6 cases
Anaplastic carcinoma of thyroid	1 case
Hürthle-cell carcinoma of thyroid	1 case
Follicular carcinoma of thyroid	1 case
Mixed papillary and follicular carcinoma of thyroid	1 case
Malignant lymphoblastoma of thyroid	1 case
Malignant tumor of neck, possibly metastatic	1 case
Hashimoto's thyroiditis	1 case

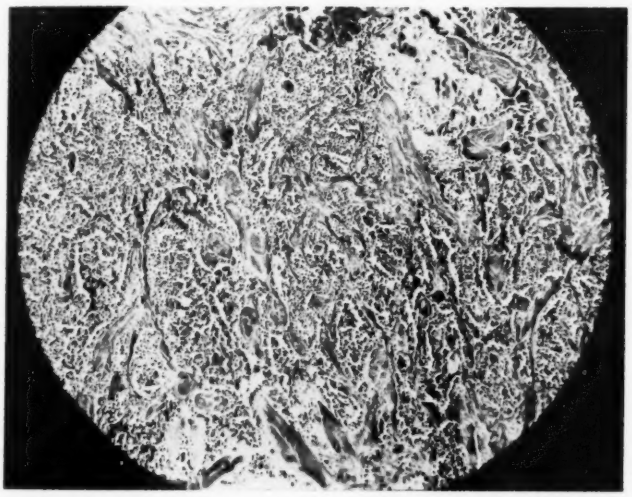

Fig. 3. Poorly differentiated follicular carcinoma of the thyroid with marked fibrous tissue infiltration, giving false negative P^{32}-uptake test. ×135

TABLE II: NEGATIVE P^{32} TESTS: NON-OPERATIVE CASES

Patients	22
Ages	28–77
Sex	17 F; 5 M
P^{32} uptake (nodule/normal)	
Mean	0.97
Range	0.81–1.12
Reason for no surgery	
Severe concurrent disease	8 cases
Obviously benign clinically	14 cases

Of the 7 patients with positive tests, 5 had an increase in uptake of P^{32} in the range of 33 to 37 per cent (Table III); in 1 the increase was 61 per cent and in 1 23 per cent. In this last patient, a previous I^{131} study may have decreased the accuracy of P^{32} counting. Malignant lesions

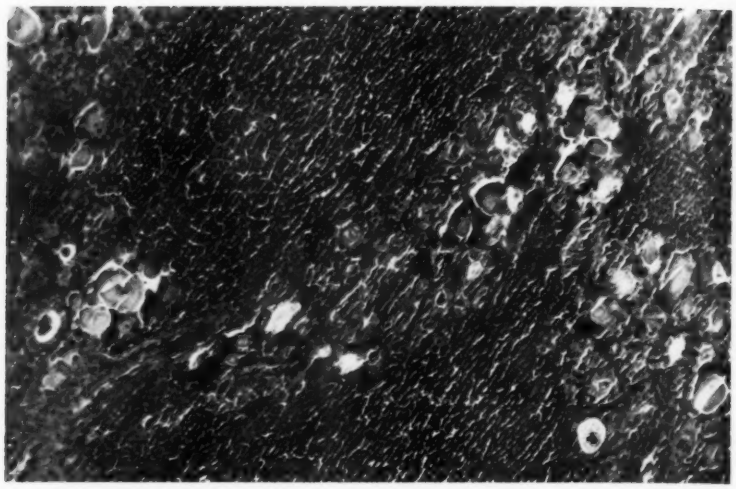

Fig. 4. Hashimoto's thyroiditis giving false positive P^{32}-uptake test. ×135

were found at surgery in 6 of the 7 patients. The one false positive occurred in a case of very cellular Hashimoto's thyroiditis not diagnosed preoperatively (Fig. 4), which had a 36 per cent increase of P^{32} uptake. The 6 malignant tumors included a rare malignant lymphoblastoma of the thyroid with a 33 per cent increase in uptake, a Hürthle-cell carcinoma with a 37 per cent increase, a follicular carcinoma with papillary elements with a 35 per cent increase, and another follicular carcinoma with a 23 per cent increase of P^{32} uptake. An anaplastic thyroid carcinoma had a 61 per cent increase. This tumor had a rapidly progressive course, terminating fatally within four months of diagnosis. Its rapid metabolic activity seemed to be reflected in the relatively high P^{32} uptake. The final patient in this series had a suspicious mass in the region of the thyroid gland. A biopsy was performed, with removal of a small section of tissue in the lateral aspect of the mass, but adequate exploration was not carried out. The microscopic sections were reported as showing "malignant tumor of neck, possibly metastatic." This patient had a 34 per cent increase of P^{32} uptake.

DISCUSSION

Although the incidence of thyroid cancer in non-toxic nodular goiters has been variously reported, the evidence is sufficient to cause one to view these lesions with some suspicion (2). In the experience of certain surgeons (Lahey, 8; Cole, 10; Cope, 3), the incidence of cancer in solitary nodules has been as high as 10 to 25 per cent. Accurate preoperative diagnosis of these lesions is often impossible with standard clinical and laboratory methods. History and physical examination may arouse suspicion in individual patients. Significant findings such as hoarseness, dysphagia, and stridor usually occur late in the disease. Other features often typical of cancer, including rapid growth, relative fixation, irregularity of shape, and hardness of the nodule, are not entirely diagnostic since they may be seen in benign lesions, especially cystic, hemorrhagic, fibrotic, and calcified adenomas. The I^{131}-uptake scan has been frequently used in the diagnosis of thyroid cancer. Appearance of cancer in the so-called "hot" nodule has been shown to be extremely rare. In the remaining nodules, those in the "warm" and "cold" categories, the cancer incidence has been reported to vary from 3 to 10 per cent for "warm" nodules and from 14 to 30 per cent for "cold" nodules (4, 5). Diagnosis of cancer in the individual patient with one of these lesions is there-

fore not possible with the I^{131} scan alone.

The use of P^{32} for the identification of malignant tissues has been in practice since the 1940's. Clinical tests for diagnosis of cancer of the eye (7), brain (12), breast (9), and stomach (1) have been devised, utilizing the increased uptake of P^{32}. Since this isotope is a pure beta emitter with a maximum depth of penetration through soft tissue of 8 mm., its use as a diagnostic tool is somewhat limited. Most lesions of the thyroid, however, are fairly superficial, and it is possible to detect beta-particle activity of the gland at the surface of the skin in most instances. Studies on excised thyroid tissue have shown that thyroid cancers have an increased P^{32} uptake as compared with normal and non-malignant diseased thyroid tissue (13).

The initial experiences with the measurement of P^{32} uptake as a method for the detection of thyroid cancer have shown difficulties in the study of a fibrotic cancer and a well differentiated cancer. Trouble is also anticipated with small or deep-seated lesions, which unfortunately are difficult to detect by any method. Inflammatory lesions of the thyroid are uncommon but do represent a possible source of false positive results. In patients with Hashimoto's thyroiditis or subacute thyroiditis, the studies may be positive because of increased cellularity and metabolic activity. The P^{32}-uptake test has been most satisfactory in the study of the solitary nodule which is discrete from the surrounding thyroid tissue, making it possible to obtain accurate counts over the lesion itself and over adjacent normal areas. Fortunately this is the type of lesion most frequently encountered for clinical evaluation. An improved method of diagnosis for such lesions would be of definite value.

SUMMARY

A technic for the diagnosis of thyroid cancer with radioactive phosphorus (P^{32}) has been developed. The patients are tested twenty-four hours after the administration of 500 microcuries of P^{32}. Counting is done with an eye-probe Geiger-Müller tube over the thyroid nodule and over surrounding areas.

A total of 61 patients were studied by this method: 7 tests were considered positive, with an increase of P^{32} uptake over the nodules ranging from 23 to 61 per cent. Six of the 7 nodules proved at operation to be malignant tumors; the seventh was a cellular Hashimoto's thyroiditis. In the 54 negative tests, the P^{32} uptakes over the nodules varied from minus 22 to plus 16 per cent. Thirty-two of the 54 patients were operated upon, and benign lesions were found in all but 2. In 1 patient the tumor was questionably malignant, probably an exceptionally well differentiated follicular carcinoma; the second patient had a follicular carcinoma with marked fibrous tissue infiltration. Twenty-two patients were not operated upon since their lesions were considered benign by clinical and laboratory evaluation.

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REFERENCES

1. ACKERMAN, N. B., SHAHON, D. B., MCFEE, A. S., AND WANGENSTEEN, O. H.: Recognition of Gastric Cancer by in Vivo Radioautography. Ann. Surg. **152:** 602–614, October 1960.

2. BEAHRS, O. H., PEMBERTON, J. DEJ., AND BLACK, B. M.: Nodular Goiter and Malignant Lesions of Thyroid Gland. J. Clin. Endocrinol. **11:** 1157–1165, October 1951.

3. COPE, O., DOBYNS, B. M., HAMLIN, E., JR., AND HOPKIRK, J.: What Thyroid Nodules Are to Be Feared? J. Clin. Endocrinol. **9:** 1012–1022, October 1949.

4. GROESBECK, H. P.: Evaluation of Routine Scintiscanning of Nontoxic Thyroid Nodules. I. The Preoperative Diagnosis of Thyroid Carcinoma. Cancer **12:** 1–5, January-February 1959.

5. JOHNSON, P. C., AND BEIERWALTES, W. H.: Reliability of Scintiscanning Nodular Goiters in Judging the Presence or Absence of Carcinoma (ab). J. Clin. Endocrinol. **15:** 865, July 1955.

6. JONES, H. B., CHAIKOFF, I. L., AND LAWRENCE, J. H.: Phosphorus Metabolism of Neoplastic Tissues (Mammary Carcinoma, Lymphoma, Lymphosarcoma) as Indicated by Radioactive Phosphorus. Am. J. Cancer **40:** 243–250, October 1940.

7. KROHMER, J. S., THOMAS, C. I., STORAASLI, J. P., AND FRIEDELL, H. L.: Detection of Intraocular Tumors with the Use of Radioactive Phosphorus. Radiology **61:** 916–921, December 1953.

8. LAHEY, F. H., AND HARE, H. F.: Malignancy in Adenomas of the Thyroid. J.A.M.A. **145:** 689–695, March 10, 1951.

9. LOW-BEER, B. V. A.: Surface Measurements of

Radioactive Phosphorus in Breast Tumors as Possible Diagnostic Method. Science **104**: 399, Oct. 25, 1946.

10. MAJARAKIS, J. D., SLAUGHTER, D. P., AND COLE, W. H.: Carcinoma of the Thyroid Gland. J. Clin. Endocrinol. **13**: 1530–1541, December 1953.

11. MARSHAK, A.: Uptake of Radioactive Phosphorus by Nuclei of Liver and Tumors. Science **92**: 460–461, Nov. 15, 1940.

12. SELVERSTONE, B., SWEET, W. H., AND ROBINSON, C. V.: Clinical Use of Radioactive Phosphorus in Surgery of Brain Tumors. Ann. Surg. **130**: 643–650, October 1949.

13. THOMAS, C. G., JR., AND WILSON, E. A.: The Uptake of P^{32} As a Measure of Cellular Metabolism in the Human Thyroid. J. Clin. Endocrinol. **19**: 306–316, March 1959.

SUMMARIO IN INTERLINGUA

Le Uso de Phosphoro Radioactive in le Diagnose de Cancere del Thyroide

Sexanta-un patientes con struma uni- o multinodular esseva examinate pro cancere del thyroide per medio de un test del acceptation vinti-quatro horas post le administration de 500 microcuries de P^{32}. Septe tests esseva considerate como positive: le augmentos del acceptation de P^{32} supra le nodulus variava in illos inter 23 e 61 pro cento. Sex del 7 nodulos esseva subsequentemente recognoscite como maligne. In le septime, il se tractava de un caso de thyroiditis cellular de Hashimoto.

In le 54 tests que esseva reguardate como negative, le acceptation de P^{32} variava inter 22 pro cento subnormal e 16 pro cento supranormal. Trenta-duo del 54 patientes esseva operate. In omnes, con 2 exceptiones, le biopsias indicava que le lesiones esseva benigne. In 1 del 2 exceptiones, le constatationes (indicante un questionabile malignitate) representava probabilemente un exceptionalmente ben differentiate carcinoma follicular. Le secunde patiente habeva un carcinoma follicular con marcate infiltration fibrose. Le remanente 22 patientes non esseva operate proque lor lesiones esseva clinicamente considerate como benigne.

Effect of L-Triiodothyronine on Post-Irradiation Fibrosis[1]

ARVIN S. GLICKSMAN, M.D., TOSHIO KITAGAWA, M.D.,[2] RALSTON R. FILLMORE, M.S., AND JAMES J. NICKSON, M.D.

THE FIRST REPORTS of radiation dermatitis followed shortly after the discovery of x-rays by Roentgen in 1895 (1). Wolbach (2) described the histopathology of radiation changes in 1909. These appear to be related to early inflammatory injury of the vascular and lymphatic structures and of connective-tissue elements, with increase in collagen. The vascular effect produces a greatly narrowed or completely occluded lumen, and thrombosis is common. An increase in the amount as well as a change in the type of collagen in irradiated tissue has been demonstrated by histologic, histochemical, and biochemical technics. These changes have been considered the major factors in the inability of irradiated tissue to heal normally and in the production of subsequent breakdown.

During the past twenty years much attention has been given to describing and modifying radiation injuries produced in living cells, tissues, and whole organisms (3, 4), with particular concentration on the period immediately before, during, and after irradiation. The general conclusion has been that any modifying agent must be present during the act of irradiation if it is to reduce injury or to foster repair. An outstanding exception was initially thought to be the administration of bone marrow or splenic cells after irradiation. But it is now accepted that the major, if not the sole, mechanism involved here is one of grafting bone-marrow cells, *i.e.*, a replacement mechanism (5).

Our group at Memorial Center demonstrated that pharmacologic doses of L-triiodothyronine (T-3) produce significant improvement in late radiation damage

Fig. 1. Normal skin and subcutaneous tissue of adult rat. Mallory trichrome. ×*c.* 125

(6). Of 75 patients with radiation injuries of two to thirty years duration, approximately two-thirds, with ulcers and fibrosis, showed good to excellent results. It was appreciated, however, that great difficulties are involved in the clinical evaluation of late radiation changes, despite attempts at objectivity, detachment, and a double-blind technic. Objective laboratory procedures were therefore developed which could quantitatively evaluate the efficacy of thyroid analogues in late radiation changes. This study covers some of the biological effects of a standard x-ray exposure and the effects of exogenous thyroid hormone on these changes.

[1] From the Departments of Medicine and Radiotherapy, Memorial Hospital, and the Section on Experimental Radiation, Sloan Kettering Institute, New York, N. Y. Presented in part at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960.

Supported in part by the U.S.P.H.S. Grant No. C-4280.

[2] Morris Fund Fellow in Radiobiology.

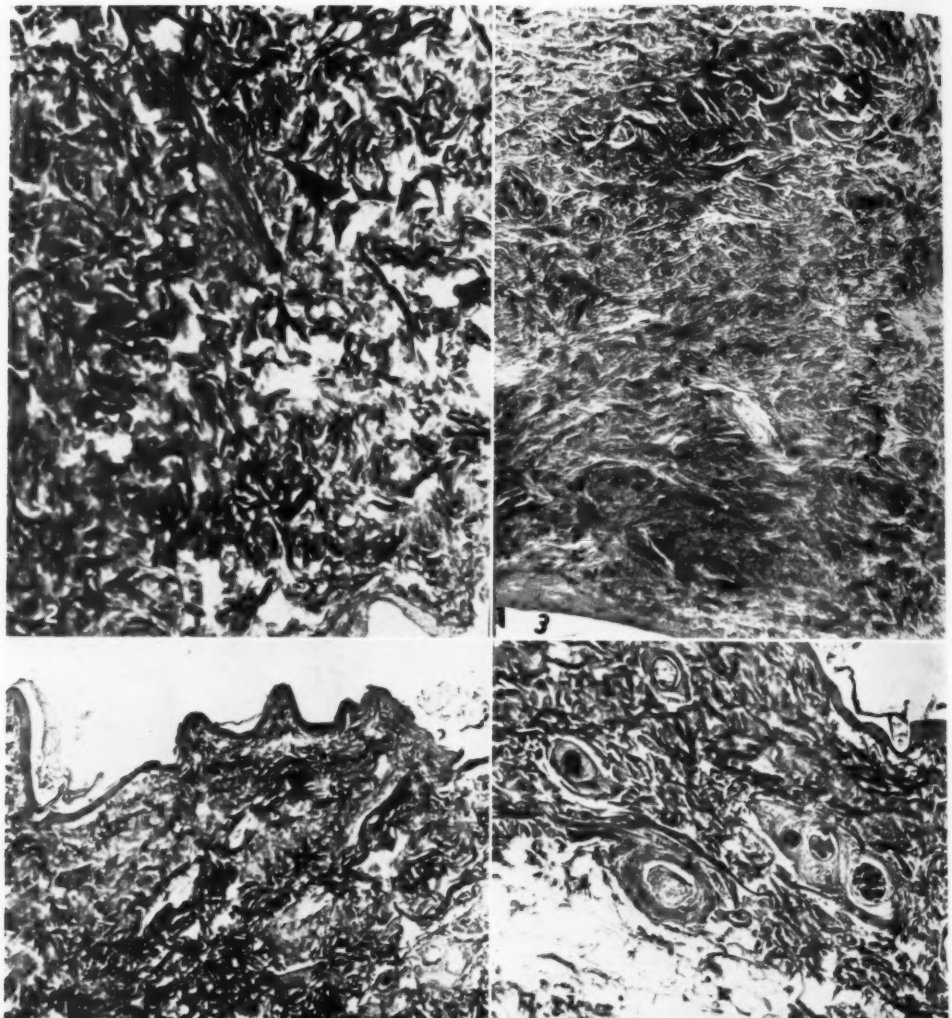

Fig. 2. Skin and subcutaneous tissue twenty weeks post-irradiation. ×*c.* 125
Fig. 3. Skin and subcutaneous tissue forty-two weeks post-irradiation. ×*c.* 125
Fig. 4. Skin and subcutaneous tissue twenty-six weeks post-irradiation; eighteen weeks on T-3. ×*c.* 125
Fig. 5. Fifty weeks post-irradiation; forty-two weeks on T-3. ×*c.* 125

METHODS

Adult male rats weighing approximately 350 to 400 gm. received 3,000 rads to the right hind limb in a single exposure from a 250-kevp x-ray generator, h.v.l. 1 mm. Cu, T.S.D. 21.5 cm., at a dose rate of 840 r per minute. The remainder of the animal was shielded from irradiation. The dose delivered to tissues outside of the direct beam was less than 5 per cent

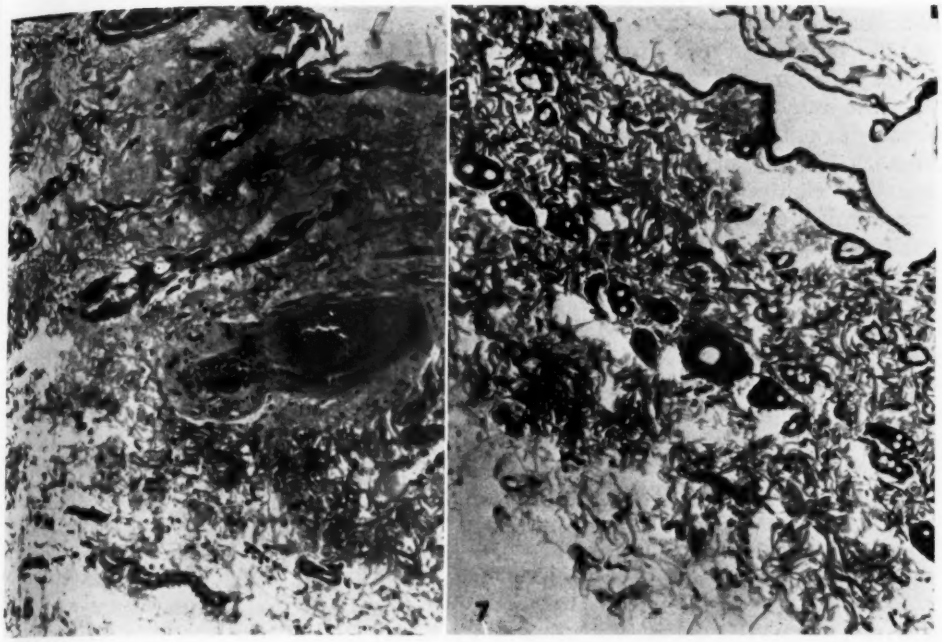

Fig. 6. Normal non-irradiated tissue after eighteen weeks of T-3 administration. ×*c.* 125.
Fig. 7. Normal non-irradiated tissue after forty-two weeks of T-3 administration. ×*c.* 125.

of that received by the right limb. Animals were randomly assigned to control groups and to a group started on L-triiodothyronine eight weeks after irradiation.

Because L-triiodothyronine was found to be stable in drinking water at room temperature for more than three days, it was given in water. Water bottles containing the drug were changed every other day to insure maximum effect of the material. The average dose was 25 micrograms per day. At monthly intervals, 3 animals from each group were sacrificed. Skin and subcutaneous tissue from both hind limbs were removed and examined by histologic, histochemical, and biochemical technics.

Histologic examination of tissue was done after preparation with hematoxylin and eosin, van Gieson, or Mallory trichrome staining technics. Mallory staining demonstrated most effectively the collagen content of the tissue, and the sections herein presented were so prepared. All sections were cut identically, were taken from essentially identical areas of sacrificed animals, and had the same magnification (×150).

RESULTS

The skin and subcutaneous tissue of a normal adult rat are shown in Figure 1. In the subcutaneous tissue is a moderate amount of loosely bound collagen. Normal skin appendages can be seen, including hair follicles and oil glands. Capillaries and small arterioles are distributed throughout the section. A small amount of subcutaneous fat is a characteristic finding.

Twenty weeks post-irradiation, an increase in the thickness of the skin and subcutaneous tissue was evident (Fig. 2). There was an increase in the amorphous collagen, with cracking of the collagen bundles. Fewer hair follicles and oil glands were found. By forty-two weeks post-irradiation (Fig. 3), extensive accumulation of collagen was apparent. Blood vessels were rarely seen, and no skin appendages were present. The subcutaneous reticular layer could not be

demonstrated in the same magnification (×150) because of the heavy accumulation of collagen.

In the animals which received T-3, the histologic pattern was appreciably different. Twenty-six weeks post-irradiation and eighteen weeks after T-3 was first administered, some accumulation of collagen and fragmentation of collagen bundles was noted (Fig. 4). However, fifty weeks post-irradiation and forty-two weeks after the first T-3 treatments (Fig. 5), the architecture of the skin and subcutaneous tissue was essentially normal. Hair follicles appeared active. Normal oil-gland and blood-vessel distribution was evident. There was a normal amount of collagen. Except for the disappearance of subcutaneous fat, normal adult tissue architecture was present.

In normal non-irradiated tissue a decrease in the collagen content could be seen after eighteen weeks of T-3 administration (Fig. 6). Forty-two weeks after T-3 was started, almost complete disappearance of normal collagen was noted (Fig. 7).

DISCUSSION

The results obtained in this study indicate that exposure to ionizing radiation accelerates the rate of accumulation of collagen. Histologically, the thyroid analogue L-triiodothyronine is seen to decrease the amount of collagen in the tissues examined. These findings may be essentially identical with those of Korenchevsky *et al.* (7), who showed that the natural involution of many organs in the aging rat could be reversed by treatment with thyroid hormones. Goldzieher (8) pointed out that many aspects of hypothyroidism and aging were similar and postulated that hypofunction of the thyroid gland may account in part for the aging process. Grad and Hoffman (9) have accumulated evidence of reduced secretion of thyroxin in the aging rat and Sobel *et al.* (10) found increased skin collagen in rats receiving propylthiouracil.

The histologic findings described here are consistent with the thesis that T-3 may modify a late sequalae of irradiation. Clinically, ulcers have healed and fibrosis has decreased or disappeared when patients were placed on pharmacologic doses of thyroid analogues. In an attempt to quantitate these histologic changes, biochemical studies of tissue have been initiated. It has been shown by Fitch *et al.* (11) that modification of the Neuman and Logan (12) method of hydroxyproline determination may afford a quantitative measure of the collagen content of tissues. The biochemical results are consistent with the histologic changes described in this paper (13).

These studies support the concept that radiation changes exist in a dynamic state and that their modification is possible by alteration of the metabolism of the damaged tissues. The mechanism by which this modification occurs is currently being investigated.

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REFERENCES

1. DANIEL, J.: The X-rays. Science **3:** 562–563, 1896.
2. WOLBACH, S. B.: Pathologic Histology of Chronic X-ray Dermatitis and Early X-ray Carcinoma. J. M. Res. **21:** 415–450, 1909.
3. BARRON, E. S. G.: Effects of X-rays on Tissue Metabolism CH-3654. University of Chicago, 1946.
4. ORD, M. G., AND STOCKEN, L. A.: Biochemical Aspects of Radiation Syndrome. Physiol. Rev. **33:** 356–386, July 1953.
5. HOLLAENDER, A., ed.: Radiation Protection and Recovery. New York, Pergamon Press, 1960.
6. GLICKSMAN, A. S., RAWSON, R. W., AND NICKSON, J. J.: Modification of Late Radiation Injury with L-Triiodothyronine. Radiology **73:** 178–190, August 1959.
7. KORENCHEVSKY, V., PARIS, S. K., AND BENJAMIN, B.: Treatment of Senescence in Female Rats with Sex and Thyroid Hormones. J. Gerontol. **5:** 120–157, April 1950.
8. GOLDZIEHER, M. A.: Endocrine Aspects of Senescence. Geriatrics **1:** 226–231, May-June 1946.
9. GRAD, B., AND HOFFMAN, M. M.: Thyroxine Secretion Rates and Plasma Cholesterol Levels of Young and Old Rats. Am. J. Physiol. **182:** 497–502, September 1955.
10. SOBEL, H., ZUTRAUEN, H. A., AND MARMOR-

STON, J.: Collagen and Hexosamine Content of Skin of Normal and Experimentally Treated Rats. Arch. Biochem. **46**: 221–231, September 1953.
11. FITCH, S. M., HARKNESS, M. L. R., AND HARKNESS, R. D.: Extraction of Collagen from Tissues. Nature, London **176**: 163, July 23,1955.
12. NEUMAN, R. E., AND LOGAN, M. A.: The Determination of Hydroxyproline. J. Biol. Chem. **184**: 299–306, May 1950.
13. KITAGAWA, T., GLICKSMAN, A. S., TYREE, E. B., AND NICKSON, J. J.: Effect of 3,5,3′ L-Triiodothyronine on Collagen Content of Irradiated and Non-irradiated Skin and Subcutaneous Tissue. Radiation Res. (In press).

SUMMARIO IN INTERLINGUA

Effecto de L-Triiodothyronina Super le Fibrose Post-Irradiatori

Esseva effectuate studios pro determinar le effecto de L-triiodothyronina super le alterationes post-irradiatori in rattos. Adulte rattos mascule recipeva 3.000 rad al extremitate dextero-posterior in un sol exposition ab un generator de radios X de 250 kevp. Le resto del animal esseva protegite contra le irradiation. Le animales esseva placiate aleatorimente in gruppos de controlo e un gruppo que comenciava reciper L-triiodothyronina octo septimanas post le irradiation.

Esseva constatate que le exposition al radiation ionisante accelerava le accumulation de collageno in le tissus. Quaranta-duo septimanas post le irradiation, grande quantitates de collageno esseva notate. Vasos de sanguine esseva vidite rarmente. Nulle appendiculos de pelle esseva apparente. Le subcutanee strato reticular non poteva esser demonstrate in le magnification de ×150 in consequentia del forte accumulation de collageno. In irradiate animales que recipeva L-triiodothyronina, un certe grado de accumulation de collageno esseva demonstrabile post dece-octo septimanas, sed quaranta-duo septimanas post le initiation del administration del droga, le pelle e le tissu subcutanee esseva essentialmente normal. In non-irradiate tissus, un quasi complete disparition del collageno normal esseva observate quaranta-duo septimanas post le comenciamento del administration de L-triiodothyronina.

Iste studios supporta le conception que alterationes per radiation progrede in phases dynamic e que lor modification es possibile per modificar le metabolismo del irradiate tissu.

Creatinuria and Fatigue in Patients Undergoing Radiation Therapy[1]

SAMUEL S. KUROHARA, M.D.,[2] PHILIP RUBIN, M.D.,[3] and LOUIS H. HEMPELMANN, M.D.[4]

THE LACK OF an objective measure of radiation sickness has obscured the definition of this syndrome. The complaints of fatigue and lassitude in patients undergoing irradiation appear to be dissociated from symptoms of nausea, vomiting, diarrhea, anorexia, and weight loss (1). This clinical observation suggests that radiation-induced myasthenia may have a mechanism of induction separate from the above gastrointestinal findings.

The rationale for studying creatinuria in radiotherapy patients is based on a number of seemingly isolated but related studies since the first observation in 1923 by Klewitz (2). The association between muscular weakness and creatinuria in muscle wasting disorders, for example, is well known. The observation of creatinuria and muscular fatigue in animals exposed to whole-body irradiation implies that a correlation exists. It is not surprising that Haberland *et al.* speculated that the creatinuria in total-body-irradiated rats and that in muscular dystrophy patients resemble each other in mechanism (3).

In this report, an attempt is made to correlate the degree of creatinuria in a heterogeneous group of patients undergoing radiation therapy for cancer with the radiation-induced symptoms and with the amount of radiation absorbed. The preliminary evidence gathered thus far substantiates the hypothesis that radiation myasthenia may be due to an alteration in creatine metabolism.

EXPERIMENTAL CONDITIONS

A. Determination of Urinary Creatine and Creatinine and Calculations: The urinary creatine was determined according to the method published previously by one of the authors (4), and the urinary creatinine by Peters' modification (5) of the Jaffe reaction. The determinations were done on 24-hour urine samples, obtained from each patient, once before therapy and at one-day to two-week intervals during its course.

Because of the possible loss of urine during collection, the 24-hour creatine values are expressed as a creatine coefficient. The following expression is slightly modified from Wilder and Morgulis (6):

$$\text{Creatine coefficient (C.C.)} = \frac{\text{Millimoles of creatine (per sample of urine)} \times 100}{\text{Millimoles of creatine (calculated as creatinine[5])} + \text{millimoles of creatinine (per sample of urine)}}$$

The degree of creatinuria is expressed as an index or ratio in order to standardize the initial values of each patient to unity (see figures). It is defined as follows:

$$\text{Creatine coefficient index (C.C.I.)} = \frac{\text{C.C. after the onset of therapy}}{\text{Initial C.C.}}$$

The rise or fall of the creatine coefficient values following the onset of treatment is expressed as the percentage change in creatine coefficient (% ΔC.C.), defined as follows:

[1] From the Divisions of Radiation Therapy and Experimental Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Presented in part at the Forty-fifth Annual Meeting of the Radiological Society of North America, Chicago, Ill., Nov. 15–20, 1959, as a Work in Progress report, published in Radiology 74: 103, 1960.

[2] Recipient of a fellowship and traineeship grant from the Public Health Service. The investigation was supported, in part, by a grant from the American Cancer Society and the U. S. Atomic Energy Commission.

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[5] The millimoles of creatine coefficient is multiplied by the factor 113/131 (molecular weight of creatinine divided by the molecular weight of creatine).

TABLE I: INFLUENCE OF THE SITE OF IRRADIATION AND SEX ON CREATINURIA AND FATIGUE

Site	No. of Cases	Average C.C.	Values % Δ C.C. (max.)	Significance of Change	Av. Max. Fatigue
Head and Neck					
Female	4	8.0	+ 33	No	±
Male	2	5.7	− 28	No	±
Thorax					
Female	4	3.9	+190	Yes	+1 to +2
Male*	5	5.2	+ 71	Yes	+2
Pelvis					
Female	12	5.9	+380	Yes	+2 to +3
Male†	6	5.8	− 14	No	±

* Borderline at the 5 per cent significance level: This group includes 2 patients who received relatively large volume doses of thoracic irradiation as compared to the others. Both had a significant degree of creatinuria.

† None of the male patients who had pelvic irradiation had any significant creatinuria. Most of them received relatively large volume doses of Co^{60} radiation, but these were not estimated to be as high as those received by the female pelvic patients.

TABLE II: INFLUENCE OF VOLUME DOSE AND SEX ON CREATINURIA AND FATIGUE

Vol. Dose Range (megagm.-rads)	No. of Cases	Average C.C.	Values % Δ C.C. (max.)	Significance of Change	Av. Max Fatigue
0–10					
Female	4	8.0	+ 33	No	±
Male	2	5.7	− 28	No	±
10–20					
Female	6	5.1	+260	Yes	+2 to +3
Male	4	6.4	+16	No	±
Over 20					
Female	11	5.7	+230	Yes	+2 to +3
Male	8	5.1	+ 35	No	±

$$\% \Delta \text{C.C.} = \frac{(\text{C.C after onset of therapy} - \text{initial C.C.}) \times 100}{\text{Initial C.C.}}$$

B. Statistical Evaluation of Laboratory Data: Because there was essentially no difference in the male and female creatine coefficients, the values of the entire group are combined to give a mean of 5.8 ± 1.9 (standard deviation).

Due to the fact that not more than one control value for 24-hour urine was available, it was impossible to evaluate the degree of creatinuria in each patient statistically. It was decided that graphical representation of the creatine coefficient index before, during, and following irradiation of a patient for a particular site, or by a particular method of irradiation, would best illustrate the degree of creatinuria. The two-tailed student *t* test is used for group comparisons (Tables I and II) at a significance level of 5 per cent.

C. Radiation Therapy: The external sources of radiation used for therapy were the (*a*) Picker Superficial X-ray, (*b*) Picker 280-kv Vanguard, (*c*) G.E. 1-Mv resonance transformer, (*d*) Picker "2000" Co^{60} teletherapy, and (*e*) 2-Mv Van de Graaff units. Standard radium and Co^{60} sources were used for intracavitary irradiation.

The specific therapy technic used for each patient depended on the particular type and location of the malignant process.[6]

D. Estimation of Tissue Integral Dose: The tissue integral dose for stationary fields (7) and intracavitary radioisotope irradiation (8) was estimated according to Mayneord's formula. The tissue integral dose for moving-beam therapy was estimated from the isodose charts. The values were obtained as follows: first, using an idealized body contour of the pelvis taken to be an elliptical cylinder; second, calculating the isodose distribution in three dimensions; third, summating the mass enclosed by the isodose surface at 10 per cent decrements multiplied by the mean per cent dose. The values, which

[6] The details as to the treatment technics can be obtained from the author.

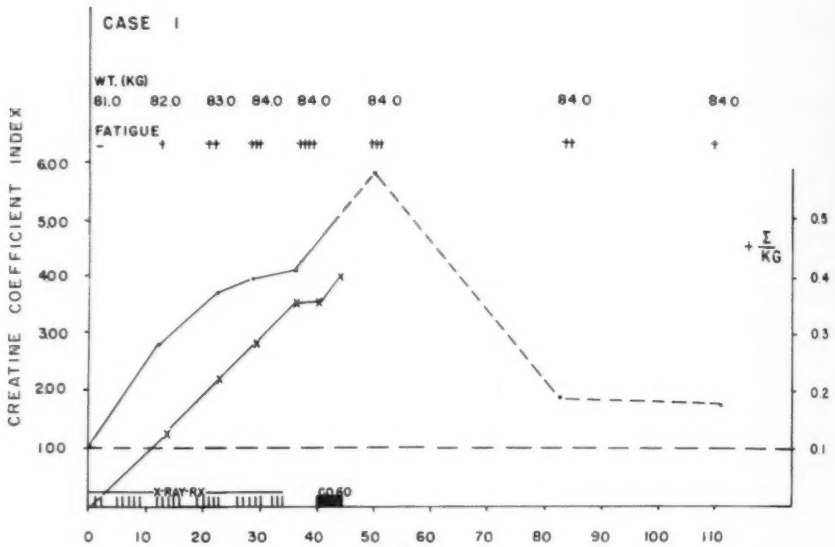

Fig. 1. The time-course of creatinuria in a representative case (I) of 1-Mev pelvic x-irradiation (solid and dotted lines). The estimated cumulative integral dose per kilogram of body weight is shown by the line adjoining the points designated by ×. The short vertical lines along the abscissa represent the daily x-ray treatments and the solid horizontal bar the Co^{60} intracavitary application.

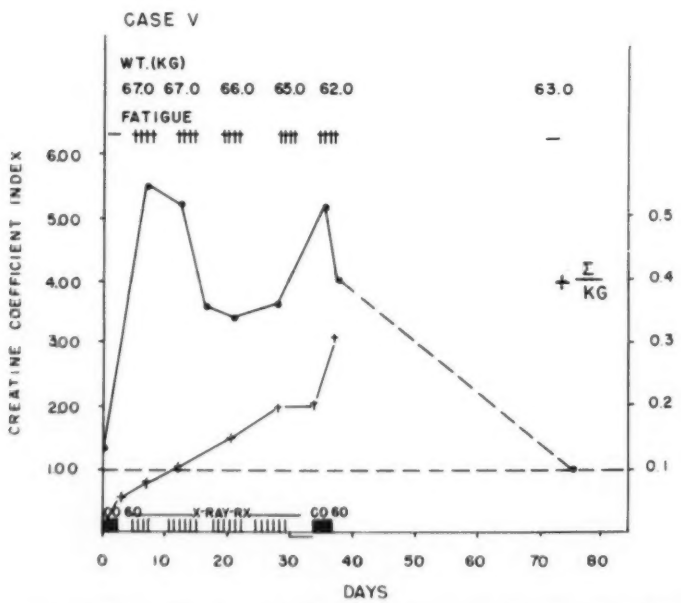

Fig. 2. The time-course of creatinuria in a representative case (V) of 280-kv pelvic x-irradiation and two Co^{60} intracavitary applications. (See explanation in Fig. 1.)

were obtained in megagram-roentgens, were converted to megagram-rads by use of the appropriate rad-roentgen conversion factors (9).

The estimates of integral tissue dose obtained by these calculations are, of course, highly theoretical and may be quite different from the true values. A discussion of the serious errors introduced by the calculation of integral dose with respect to the quality of radiation, field size, and depth of tissue can be found in the literature (10). Because of the many uncontrollable factors and the variability in the treatment technics, no direct measurements of integral dose were carried out in this study. The patients in Table I are grouped in volume dose ranges, namely 0–10, 10–20, and over 20 megagram-rads.

E. Evaluation of Symptoms: The patients were interviewed carefully as to their complaints near the time of urine collection. The symptoms were then evaluated and graded subjectively on the following basis: 1+, mild; 2+, moderate; 3+, severe; 4+, extremely severe; ±, equivocal; 0, no symptomatology.

CLINICAL OBSERVATION

A. Site of Irradiation

Group I. Pelvic Irradiation: (a) in females: The peak values for creatine excretion occurred in all cases before the completion of therapy, except in Case I. In most of the females who received radiation to the pelvis, the creatine coefficient increased by a factor of 2 to 6 times the initial value. Table I shows the average initial and maximal percentage change in creatine coefficient for this group. The difference between these values is significant. On the average, these patients complained of moderate to severe fatigue symptoms during the course of treatment.

CASE I: A 72-year-old female with a Stage II carcinoma of the cervix showed the greatest degree of creatinuria in this group (Fig. 1). Curiously, the peak of creatinuria occurred following the completion of intracavitary irradiation. This correlated reasonably well with the patient's fatigue symptoms, which also were most severe at the end of the course of therapy. She gained weight throughout the treatment period, ruling out simple wasting or weight loss as a factor. As strength returned gradually, the creatine coefficient returned to base-line values.

Nine patients received intracavitary Co^{60} or radium pelvic irradiation in addition to a course of external beam therapy. Their average per cent increase in creatine coefficient was definitely greater during the first application (+190 per cent) than during the second (+130 per cent). The degree of fatigue in these patients did not appear to differ markedly in severity during the two treatment periods.

There was a striking similarity in the pattern of creatinuria in the 3 patients who were treated by our standard radiation technic for Stage I carcinoma of the cervix. The pattern consisted of two major peaks corresponding in time with the application of intracavitary sources. The plot of the creatine coefficient index and the cumulative integral dose per kilogram in a representative case (Fig. 2) shows that large continuous volume doses received during intracavitary irradiation may be important.

The creatine coefficients of 3 patients who had dilatation and curettage under general anesthesia were obtained on the first, second, and fourth day following the operative procedure, as a control group for the patients who had received intracavitary irradiation treatments. Their creatine coefficient values were ranging at normal levels, between 5.0 and 7.5.

CASE V: A 67-year-old female with early Stage I cervical carcinoma showed peak values of creatinuria following each intracavitary application (Fig. 2). The early onset of fatigue and its persistence during the 280-kv irradiation fits well with the elevated creatine coefficient index during therapy. The return of creatine excretion to pretherapy values in one month, with absence of fatigue at this time, is a most impressive correlation.

Pelvic Irradiation: (b) in Males. Supervoltage Therapy Only: The male patients treated for pelvic neoplasms with the Co^{60} teletherapy unit showed a significant rise in neither the creatine coefficient nor fatigue symptoms. Even though the pel-

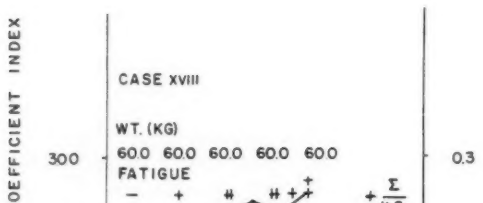

Fig. 3. The time-course of creatinuria in a representative case (XVIII) of 1-Mev thoracic x-irradiation. (See explanation in Fig. 1.)

vic fields utilized in cobalt teletherapy were smaller than those used in the pelvic supervoltage irradiation of female patients, the tissue integral doses may have been as great, due to the larger penumbra. Nevertheless, the urinary creatine excretion in males is more stable and has less of a tendency to show spontaneous rises. It is suggested that differences in creatinuria may be due to hormonal factors which will be elaborated later. If a larger volume dose of radiation is administered, as in some of the thorax-irradiated patients, a significant rise in their creatine coefficient does occur.

Group II. Thoracic Irradiation: (*a*) *in Females:* Three of the 4 female patients in this group were irradiated postoperatively for carcinoma of the breast; 1 was irradiated for mediastinal Hodgkin's disease. All showed a significant rise in creatine excretion, but not as large as that of the females irradiated for pelvic cancer (Table I). The fatigue symptoms were also milder.

CASE XVIII (Fig. 3): A patient with postoperative carcinoma of the breast received radiation through supraclavicular and internal mammary fields, for a total of approximately 15 megagram-rads in thirty-two days. The peak creatinuria (twice the initial value) occurred one and a half weeks before treatments were completed. There was moderate fatigue at that time. On completion of therapy, creatine excretion had returned to baseline levels. Fatigue complaints had also improved.

Thoracic Irradiation: (*b*) *in Males:* Three of the 5 male patients receiving thoracic irradiation were treated through large fields. Two of them showed a significant increase in creatine coefficient as well as an increase in fatigability. The 2 in whom relatively small fields were used did not show any significant degree of creatinuria or fatigability. The difference between the mean initial and maximal creatine coefficient values of this group were barely significant (Table I).

Group III. Abdominal Irradiation: The creatine excretion was followed in only 2 cases of abdominal irradiation. In the male patient there was no remarkable rise in creatine excretion or increased fatigue. Although the female patient showed a greater rise than the male, it was not as great as for the pelvic-irradiated females despite irradiation of the entire abdomen and pelvis. This may be due to the small fractionated doses used over longer periods of time.

Group IV. Head and Neck Irradiation: The changes in creatine coefficient values were relatively small and inconsistent (Table II) in patients receiving irradiation to the head and neck. Fatigue symptoms were absent or equivocal in this group.

CASE XXXI (Fig. 4): A female patient was treated with the 280-kv Vanguard unit for pituitary chromophobe adenoma, receiving approximately 8 megagram-rads in forty-one days. She had essentially no fatigue symptoms and the rise in percentage creatine coefficient values was insignificant.

B. Volume Dose

Table II shows the mean initial and maximal percentage changes in creatine coefficient values and the average estimates of the maximal degree of fatigue developing during the course of therapy in the female and male patients, grouped according to three broad ranges of total volume dose. It is apparent that the only significant increase in creatinuria was seen in the female patients who received a volume dose above 10 megagram-rads. They complained of the most severe fatigue during their treatment course. Only 2 male patients showed a significant rise in

creatinuria and complained of severe fatigue. They received treatments to the entire thorax and neck, with lungs shielded throughout most of the therapy course.

C. Sex

The male patients generally showed a smaller rise in creatine coefficient, despite the administration of large integral doses (Table II). Their fatigue symptoms were usually minimal. The difference in the degree of their responses to irradiation is evident.

DISCUSSION

The many uncontrollable factors such as treatment technic, time-dose relationship, quality of radiation, and the clinical status of the patient make the analysis of the data difficult. Except for Case VII, any patient who was found to have an illness which has been said to be associated with creatinuria was excluded from the study. In Case VII rheumatoid arthritis of the hands was present but was so mild that it seems likely that it had little or no effect on the observed creatinuria (11). The treatment technics, time-dose relationships, and the quality of radiation used were governed by the nature of the patient's malignant disease. For example, the anatomical location and extent of the lesion determined such treatment factors as the number of fields, field size, method of application (moving or stationary beam therapy), and the quality of the radiation. The histologic nature and volume of normal tissue irradiated governed the time-dose factor, etc.

Of the various possibilities that lead to excessive creatine excretion, the following deserve special consideration in the present study: (1) inadequate diet and fasting state; (2) wasting diseases, as advanced carcinoma; (3) leakage or decreased uptake of synthesized creatine by muscle; (4) decreased tubular absorption of creatine; (5) stress and stimulation of pituitary-adrenal axis.

Inadequate Diet and Fasting States: Creatine values may be elevated in the urine

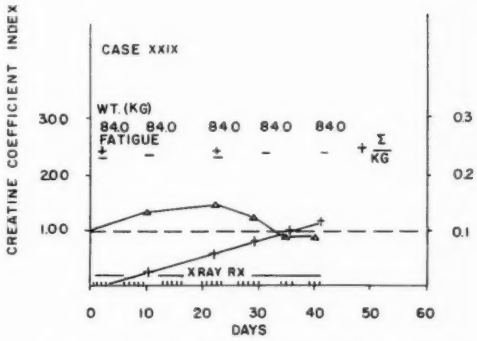

Fig. 4. The time-course of creatinuria in a representative case (XXIX) of head and neck x-irradiation (280 kv). (See explanation in Fig. 1.)

of normal subjects maintained on a low carbohydrate diet during fasting periods (12), presumably due to excessive catabolism of muscle tissue. The common findings of anorexia and low food intake due to radiation therapy must be excluded as factors in creatinuria. As Court-Brown and others have observed, radiation sickness encountered in clinical practice appears to be dissociated into two major components: muscular fatigue symptoms and gastrointestinal symptoms (1). This has been borne out in our experience.

Few patients in the pelvic-irradiated group had digestive complaints of major proportions. In fact, in Case I, with the highest creatine coefficient, there was a gain of 2.5 kg. during the treatment period. The gradual loss in weight in patients receiving orthovoltage and intracavitary irradiation (Fig. 2) is related to the anorexia but does not seem to be associated with the creatinuria, which showed an earlier peak and clearly followed the rate of dosage delivered from intracavitary cobalt. The persistent weight loss in the head and neck cases did not result in an excessive excretion of creatine. Only after severe inanition has creatinuria been reported (13). Thus, it is dubious whether diet was an important factor in the creatinuria detected.

Wasting Diseases Such as Advanced Carcinoma: The associated muscular wasting in cancer patients may lead one to

postulate this as a cause of creatinuria. This was obviated by base-line studies prior to irradiation. During therapy, the tumor regresses and the malignant process is checked when the elevation of the creatine coefficient occurs. The patient in Figure 2 had an early Stage I lesion of the cervix, further negating uncontrolled carcinoma as a major factor in producing creatinuria. The decreased physical activity due to fatigue is probably of little importance, as creatinuria occurs only after complete immobilization of about one week (14).

Leakage or Decreased Uptake of Synthesized Creatine by Muscle: Creatinuria is a consistent finding in muscle wasting disorder, *e.g.*, muscular dystrophies, poliomyelitis, etc. (15). The various mechanisms proposed are, in brief: (*a*) increased synthesis of creatine by the liver; (*b*) creatine leakage from muscle stores; (*c*) decreased uptake of synthesized creatine by the muscle; (*d*) increased production or release through unknown routes. Isotopic studies in patients with muscular dystrophy suggest that their creatinuria is due to the failure of uptake by muscle of normally synthesized creatine. Comparable studies done in single-dose total-body irradiated rats indicate a similar mechanism in their radiation myopathy (3). It seems reasonable to explain the good correlation between the degree of creatinuria and fatigue on the basis of the tissue (muscle) integral dose. That is, the larger the mass of muscle injured, the less will be the uptake of normally synthesized creatine and, therefore, the greater the spillage of creatine into the urine. This may be a factor in the finding of the greatest degree of creatinuria in patients undergoing pelvic irradiation as compared to other anatomical sites involving less muscle mass.

Decreased Tubular Absorption of Creatine: A decrease in the tubular resorption of creatine secondary to aminoaciduria appears to be an unlikely explanation, since the plasma amino acid concentration required to produce a significant depression must be relatively high (16). Aminoaciduria reported in man and in animals even after total-body exposures are at variance. Furthermore, since creatine is a threshold substance, and since there is a rise in plasma creatine level concomitantly with creatinuria in whole-body irradiated rats (17), the mechanism of renal overflow would be a more likely possibility.

Stress and Stimulation of the Pituitary-Adrenal Axis: One confusing subject of discussion is the relationship of the hormonal system, the pituitary-adrenal axis in particular, to radiation sickness and to creatinuria. The adrenal glands of total-body irradiated animals (18) show histologic and biochemical changes similar to those seen in animals after ACTH administration (19). Creatinuria has been reported in other conditions of severe stress, as in fractures (20), burns (21), and fever (22), and also in patients given relatively large doses of ACTH or cortisone (23). The renal tubular resorptive mechanism of creatine is shown to undergo diminution in patients treated with DOCA and in patients with Cushing's disease (24). In patients undergoing radiotherapy, changes in adrenal function have been shown by Lasser and Stenstrom (25) to occur, by means of the absolute eosinophil count and the Thorn ACTH eosinophil response tests. These authors did not indicate, however, that radiation sickness is due purely to adrenal response. In hypophysectomized and thyro-parathyroidectomized rats, no significant creatinuria occurs after total-body exposure to radiation (26). For this reason the control group of anesthetized patients undergoing dilatation and curettage, patients presumably under some stress, were studied. No striking elevation in creatine excretion occurred, suggesting that the peak of creatinuria occurring after radioactive cobalt is placed in the uterus is not due to stress produced by the procedure but probably related to the amount of radiation absorbed.

The influence of ovarian hormones should also be considered, since there is a

striking difference between the male and the female, and since the administration of estrogenic hormones in man has been reported to invoke creatinuria (27). The presence of post-irradiation creatinuria in Cases IV and X, following total hysterectomy and bilateral salpingo-oophorectomy, indicates that the ovaries are of minor importance and that the differences in the degree of creatinuria must be explained by other hormonal mechanisms. Furthermore, it should be noted that most of our patients were past the menopause.

It is evident that much further work is required to elucidate the mechanism of creatinuria and associated radiation symptoms. Toward this end we are doing animal experiments simulating the partial-body radiation treatments of patients and using isotopic labeled creatine and precursor substances to study the alterations in creatine metabolism which occur under these conditions. With the development of objective parameters to measure the degree of radiation sickness, the mechanism of its production will be better appreciated and may ultimately lead to the development of effective drugs to remedy this condition.

SUMMARY

1. The 24-hour urinary creatine levels were measured at daily to weekly intervals in 35 patients who were treated for various types of malignant disease.

2. The degree of creatinuria appeared to be related to the severity of fatigue symptoms, tissue integral dose, the sex of the patient, and the anatomical site of irradiation.

3. The greatest increases in the creatine coefficient values were found during the course of irradiation in female patients who received radiation therapy to the pelvis. This appeared to be related to the integral dose and the treatment time in which the radiation was absorbed.

4. The male patients who received pelvic irradiation did not show any significant degree of creatinuria or fatigue symptoms.

5. The patients who received relatively large volume doses to the thorax showed a significant degree of creatinuria and fatigue.

6. The fatigue symptomatology and the degree of creatinuria appeared roughly to parallel each other. The most severe fatigue symptoms occurred at the height of creatinuria or just following it. The female patients who received radiation to the pelvis suffered more fatigue than the patients who received radiation to the abdomen, thorax, or head and neck region.

7. The need for redefinition of clinical radiation sickness into two types of symptoms, (*a*) gastrointestinal and (*b*) muscular fatigue, is emphasized.

8. Various possible mechanisms of creatinuria are discussed.

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REFERENCES

1. COURT BROWN, W. M.: Symptomatic Disturbance after Single Therapeutic Dose of X-rays. Its Relationship to General Radiation Syndrome. Brit. M. J. **1**: 802–805, April 11, 1953.

2. KLEWITZ, F.: Kurze Mitteilung über einige Stoffwechseluntersuchungen bei Röntgenbestrahlungen (Kreatinin-Kreatin-Aminosäuren und Stickstoffausscheidung). Strahlentherapie **14**: 101–105, 1923.

3. HABERLAND, G. L., AND OTHERS: Creatine-Creatinine Metabolism in Radiation Myopathy. Nature, London, **175**: 1039–1040, June 11, 1955.

4. KUROHARA, S. S.: Determination of Urinary Creatine. Clin. Chem. **7**: 284–288, August 1961.

5. PETERS, J. H.: Determination of Creatinine and Creatine in Blood and Urine with the Photoelectric Colorimeter. J. Biol. Chem. **146**: 179–186, November 1942.

6. WILDER, V. M., AND MORGULIS, S.: Creatinuria in Normal Males. Arch. Biochem. **42**: 69–71, January 1953.

7. MAYNEORD, W. V.: Measurement of Radiation for Medical Purposes. Proc. Phys. Soc. London **54**: 405–421, September 1942.

8. MAYNEORD, W. V.: Energy Absorption. Brit. J. Radiol. **13**: 235–247, July 1940.

9. MURPHY, W. T.: Radiation Therapy. Philadelphia, W. B. Saunders Co., 1959, p. 4.

10. BEWLEY, D. K., BATCHELOR, A. L., LOWE, J., NATAADIDJAJA, E., NEWBERY, G. R., AND OPIE, R.: Integral Doses at 200 kv and 8 mev. Brit. J. Radiol. **32**: 36–46, January 1959.

11. DAWSON, J. E., AND SALT, H. B.: Creatine Metabolism in Arthritis. Ann. Rheumat. Dis. **11**: 23–28, March 1952.

12. ORD, M. G., AND STOCKEN, L. A.: Creatine and Carbohydrate Metabolism. Biochem. J. **59**: 272–279, February 1955.

13. THOMSEN, A.: Kreatinuri. Copenhagen, 1938.

14. HEILSKOV, N. S. C., AND SCHØNHEYDER, F.: Creatinuria Due to Immobilization in Bed. Acta med. scandinav. **151:** 51–56, 1955.

15. PETERS, J. P., AND VAN SLYKE, D. D.: Quantitative Clinical Chemistry Interpretations. Baltimore, Williams & Wilkins Co., 2d Ed., 1946, Vol. I, pp. 897–936.

16. PITTS, R. F.: Renal Reabsorptive Mechanism in Dog Common to Glycin and Creatine. Am. J. Physiol. **140:** 156–167, November 1943.

17. WILLIAMS, C. M., KRISE, G. M., ANDERSON, D. R., AND DOWBEN, R. M.: Post-irradiation Creatinuria in the Rat. Radiation Res. **7:** 176–183, August 1957.

18. PATT, H. M., AND BRUES, A. M.: The Pathological Physiology of Radiation Injury in the Mammal. II. Specific Aspects of the Physiology of Radiation Injury. [In] Radiation Biology, edited by Hollaender, A., with the cooperation of Brues, A. M., and others. New York, McGraw-Hill Book Co., Inc., 1954, pp. 959–1028.

19. SAYERS, G.: Adrenal Cortex and Homeostasis. Physiol. Rev. **30:** 241–320, July 1950.

20. CUTHBERTSON, D. P., MCGIRR, J. L., AND ROBERTSON, J. S. M.: Effect of Fracture of Bone on Metabolism of Rat. Quart. J. Exper. Physiol. **29:** 13–25, March 1939.

21. CLARK, E. J., PETERS, R. A., AND ROSSITER, R. J.: Nitrogen Metabolism after Burning. Quart. J. Exper. Physiol. **33:** 113–121, March 1946.

22. WANG, E.: Clinical and Experimental Investigations on the Creatine Metabolism. Acta med. scandinav. Suppl. 105, 1939, pp. 1–338.

23. SPRAGUE, R. G., AND OTHERS: Observations on Physiologic Effects of Cortisone and ACTH in Man. Arch. Int. Med. **85:** 199–258, February 1950.

24. ZIERLER, K. L., FOLK, B. P., MAGLADERY, J. W., AND LILIENTHAL, J. L., JR.: On Creatinuria in Man. Roles of Renal Tubule and of Muscle Mass. Bull. Johns Hopkins Hosp. **85:** 370–395, November 1949.

25. LASSER, E. C., AND STENSTROM, K. W.: Radiation Sickness: A Study of its Relation to Adrenal Cortical Function and the Absolute Eosinophil Count. Am. J. Roentgenol. **72:** 474–487, September 1954.

26. KRISE, G. M., AND WILLIAMS, C. M.: Hormonal Factors Influencing Postirradiation Creatinuria and Polyuria in the Rat. Am. J. Physiol. **196:** 1352–1355, June 1959.

27. WHEDON, G. D., AND SHORR, E.: Metabolic Studies in Paralytic Acute Anterior Poliomyelitis. IV. Effects of Testosterone Propionate and Estradiol Benzoate on Calcium, Phosphorus, Nitrogen, Creatine, and Electrolyte Metabolism. J. Clin. Invest. **36:** 995–1033, June (Part 2), 1957.

SUMMARIO IN INTERLINGUA

Creatinuria e Fatiga in Patientes Subjicite a Therapia Radiatori

Le quantitates de creatina in le urina de 24 horas esseva mesurate a intervallos de inter un die e un septimana in 35 patientes sub tractamento pro varie typos de morbo maligne.

Le grado de creatinuria pareva esser relationate con le severitate del symptomas de fatiga, le dose integral al tissu, le sexo del patiente, e le sito anatomic de irradiation. Le plus marcate augmentos in le valores del coefficiente de creatina esseva trovate in le curso del irradiation in patientes feminin qui recipeva therapia irradiatori al pelve. Isto pareva esser relationate con le dose integral e le tempore del tractamento durante le qual le radiation esseva absorbite. Le patientes mascule qui recipeva irradiation pelvic non manifestava ulle significative grado de creatinuria o de symptomas de fatiga.

Le patientes qui recipeva relativemente grande doses al thorace monstrava un grado significative de creatinuria e de fatiga.

Le symptomatologia del fatiga e le grado de creatinuria pareva esser grossiermente in parallela. Le plus sever symptomas de fatiga occurreva al culmine del creatinuria o justo post illo. Le patientes feminin qui recipeva radiation al pelve suffreva plus fatiga que le patientes irradiate in abdomine, thorace, e le region de capite e collo.

Varie mechanismos possibile pro le creatinuria es discutite, sed studios additional es requirite.

A Patient Propulsion Procedure for Aorto-Arteriography[1]

RUSSELL WIGH, M.D., WILLIAM F. LINDSEY, M.D., JACK MORGAN, B.S., and WINFORD H. POOL, JR., M.D.

THE DEVELOPMENT OF vascular surgery has required that suitable radiographic procedures be available to illustrate the pathologic or congenital abnormalities present, as well as to give further information relating to altered hemodynamics. The proper planning of a surgical approach is partially dependent on knowledge gained in these areas by radiologic methods. Such procedures are of great use, also, in separating abnormalities not yet amenable to surgical correction.

Many methods have been designed for peripheral arteriography and for abdominal aortography since Dos Santos (1) introduced this as a clinical procedure in 1929. Reviews and discussions of the methods have been numerous; briefly, the technics consist of single long-film exposures or serial long-film exposures, multiple combinations of 14 × 17-inch films, or scanography (2–6).

In plans for new x-ray departments or revisions of existing areas, consideration is generally given to the purchase of apparatus for cardiac angiography, but infrequently to the acquisition of specific equipment for peripheral arteriography. This situation arose in our own institution.

The procedure that we have selected and have developed consists essentially of moving the patient over a serialographic film changer, the rate of movement and the intervals of exposure being known. Earlier efforts in this direction have been made by Christmann (7) and Ellzey (8). The selection was not dictated solely because of possible superiority over other existing methods. The object was to determine whether or not the versatility of previously installed, expensive, specialized equipment (angiocardiographic) could be increased, as well as to reduce the costs that would be necessitated by employing still further "special equipment" such as built by Eyler (2) or manufactured for this purpose. The interrelationship of this project with other developments utilizing the same basic equipment is described elsewhere (9).

Many radiological departments now have serialographic film changers with a suitable width of coverage to expose both femoral areas simultaneously. These might be used, as will be illustrated, for aorto-arteriography in continuity. The additional expense is small.

EQUIPMENT

The general equipment is illustrated in Figure 1. Its major component is the horizontal plane of a biplane roll film changer; this is placed at the foot of a radiographic table. A Formica-covered plywood platform, measuring 8 × 2 feet, and 1 inch thick, is suspended over the changer with one end resting on the x-ray table and the other on a simple metal stand. An aperture, the size of the film exposure area, has been cut in this platform in the appropriate place. Two wooden guide-bars run the length of the table; they are separated by 20.5 inches. A Schönander table top (TIT-23), consisting of a Bakelite panel 6 feet long and 20 inches wide, with rollers on its under side, fits between the guide-bars of the plywood platform. One attaches to the more accessible side of the Bakelite table a 6-foot length of steel gear track, 3/4 × 3/4 inch, with gear teeth to match a 16-pitch gear drive assembly. A reversible 0.06 horsepower alternating current series-type motor with a 100-1 gear reduction box is fastened to the plywood platform in such fashion that the gear drive assembly engages the gear track attached to the movable table (Fig. 2).

The forward and reverse motion and the

[1] From the Department of Radiology, Medical College of Georgia, Augusta, Ga.
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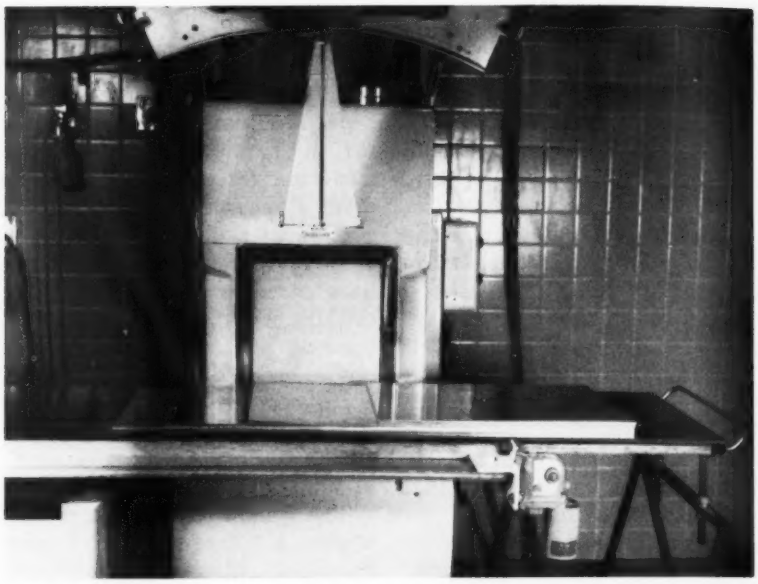

Fig. 1. The equipment utilized to transport the patient over the film exposure area of a serialographic unit. A motor-driven table-top mounted on a platform suspended between the radiographic table and a metal stand bridges the horizontal roll film changer.

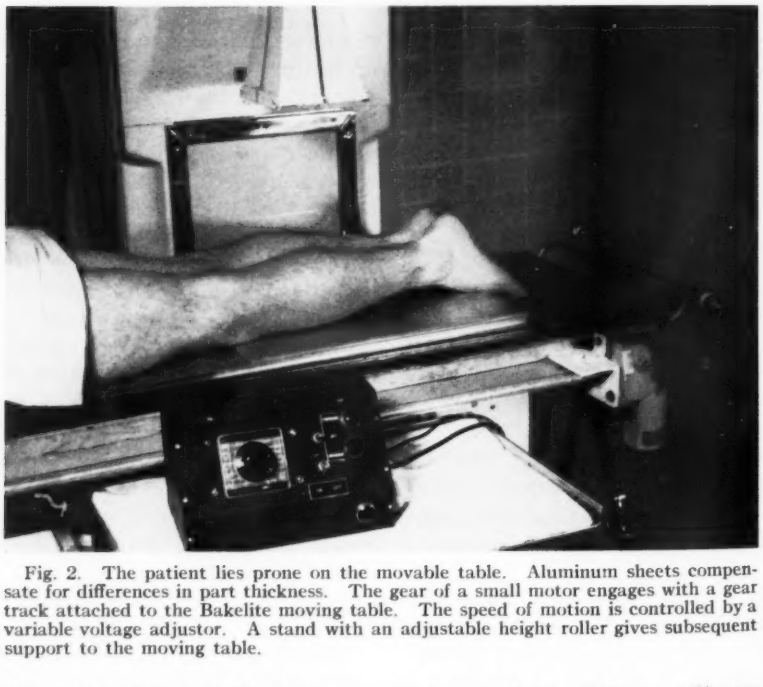

Fig. 2. The patient lies prone on the movable table. Aluminum sheets compensate for differences in part thickness. The gear of a small motor engages with a gear track attached to the Bakelite moving table. The speed of motion is controlled by a variable voltage adjustor. A stand with an adjustable height roller gives subsequent support to the moving table.

speed of the motor-driven table top are controlled by a portable box containing a double-pole, double-throw reversing switch and a variable voltage adjustor with an input voltage of 115 volts and an output voltage of 0-130 volts.

As the patient and rolling table move away from the support of the stationary plywood platform, additional support is derived from a second iron stand (Schönander #TIB-1). This stand has mounted above it an adjustable-height roller which fits between the wheels of the moving Bakelite table and permits smooth continuing motion (Fig. 2).

EXPERIMENTAL BACKGROUND AND MOTION DATA

Table Motion and Exposure Time: The specific room in this instance is equipped with Dynapulse units with pulse lengths between 1 and 5 milliseconds. The initial experimental work with dogs was done with such short exposures, since it was thought that with usual exposure times the table motion would have to be stopped for the exposure, and this would have required a braking and releasing attachment for the moving table. Millisecond timing was found subsequently not to be needed. Actually, if the method could be used only under such millisecond circumstances, its general adoption would be limited to very few departments. At the present time, also, for voltages that are in general use, the method would fail for the very heavy patient (satisfactory abdominal exposures at 5 milliseconds and 120 kv cannot be obtained above a part thickness of about 30 cm.).

With conventional timing, it is found that with uninterrupted motion of the table, an exposure of 1/60 second will not result in blurring up to a travel range of 4 inches per second. With an exposure of 1/30 second, a travel range of 3 inches per second can be achieved. In clinical work a selection of 1/30 second for exposure timing at 500 ma has been found preferable because it permits selection of lower kilovoltage technics. Other conditions of this test included: high-speed film, high-speed screens, a linear grid with a ratio of 12:1, and a target-film distance of 36 inches.

Speed and Weight: On the graph in Figure 3 there is plotted the speed of motion of the table in inches per second for various applied voltages on the motor for the assembly described. Other accumulated data showed that, for patient weights between 100 and 200 pounds, there is no significant change in the rate of speed of this table. A preselected voltage setting will therefore move the table at a required speed.

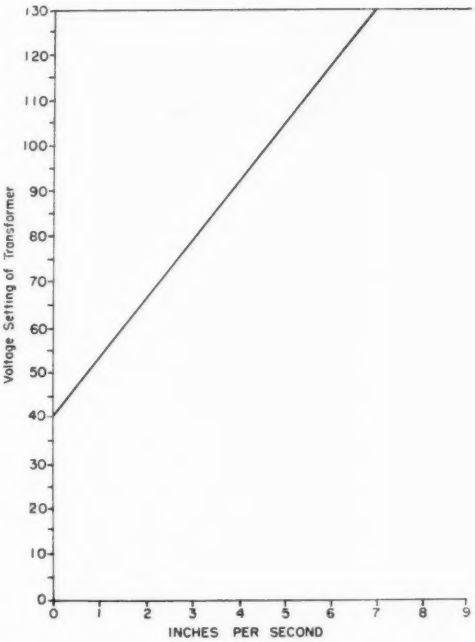

Fig. 3. Graph plotting the speed of motion against the voltage setting of the transformer. For patient weights between 100 and 200 lb. there is no significant change in speed.

Variations in Body Thickness: In technics employing a single long film, a graduated filter can be placed in front of the tube to compensate for the considerable changes in the thickness between abdomen and lower extremities. In still other methods, screens of different speeds can be selected. The effects of one of the intensifying screens can be blocked out by inserting paper in back of the film. Ellzey altered the exposure time between roentgenograms in his manual method of pushing and stopping the table.

Compensation for body thickness with this continuous patient propulsion technic

Fig. 4. A–G. A series of films demonstrating aorto-arteriography in continuity. Table motion is cephalad in direction. There is a three-second interval between exposures, during which the table has moved 6 inches. These films were made from five to twenty-four seconds from the beginning of aortic injection. See also Fig. 4. H-I.

cannot be obtained through a stationary wedge filter attached to the tube housing. It can be obtained by adding material to thinner portions of the body. Our first effort to obliterate this variable, consisted in the construction of a special wedge of unit density Masonite which was inserted under the lower extremities. Such a wedge produces magnified distortion and some loss of detail, particularly in the legs. Because of these factors, but primarily because of confusing artefacts due to the laminated construction, this Masonite method of part-thickness compensation was discarded.

Aluminum sheets are now employed.

Fig. 4. H–I. A portion of the *reverse propulsion* exposures made at twenty-seven and thirty seconds. At later intervals (*i.e.*, thirty-three seconds), on more proximal exposures, the opaque medium was no longer present.

One will find that 1.5 to 2.0 mm. of aluminum will compensate for each centimeter of body tissue difference. It is preferable to select the smaller factor for the thigh and knee areas. In the lower calf and ankle regions, better uniformity is achieved by adding 2 mm. of aluminum for each additional centimeter of tissue difference. It is not necessary to carry the aluminum to the trunk area above the buttock crease.

Table I shows the amounts and positions of added aluminum in reference to thickness of parts in two patients of different habitus. Measurements are more useful at the buttock crease, mid-thigh, knee, calf, and ankle. Inspection of the general contours of the patient readily indicates which of these regions should be selected for measurement. Actually, a shortened test run is still used; the films are checked for technic, and the aluminum compensation is varied if necessary.

TABLE I: ALUMINUM COMPENSATION FOR VARYING TISSUE THICKNESSES

Part	Patient I		Patient II	
	Tissue Thickness, (cm.)	Added Aluminum, (mm.)	Tissue Thickness, (cm.)	Added Aluminum, (mm.)
Abdomen	18	...	23	..
Buttocks	17	...	24	..
Upper thigh	..	10.5	17	9
Mid thigh	11	10.5	14	14
Lower thigh	..	10.5	..	14
Knee	8	15	12	18
Calf	8	15	..	18
Ankle	7	21	7	26

PROCEDURE

The procedure used at present is considered the best of several that have been tried. The patient is placed prone on the movable table top, the amount of aluminum sheeting having been predetermined. The table is initially positioned over the Potter-Bucky tray in the radiographic table. After the insertion of a 17-gauge needle in the abdominal aorta, 10 c.c. of opaque medium is injected. A preliminary exposure is made to ascertain that the tip of the needle is properly placed within the aorta and at a level beneath the origins of the renal arteries. After inspection of this film, the rolling table is so placed that the abdomen of the patient is over the exposure area of the film changer.

Forty cubic centimeters of 75 per cent sodium diatrizoate (Hypaque) mixed with 4 c.c. of 2 per cent procaine is injected over a period of ten seconds. At an elapsed time of five seconds following the beginning of the injection, the first serialographic exposure is made. Immediately after the fifth second patient propulsion is begun and the remaining radiographs are made at intervals of three seconds. As a consequence, table motion (patient propulsion) and exposures begin almost simultaneously, when only half of the total volume of opaque medium has been

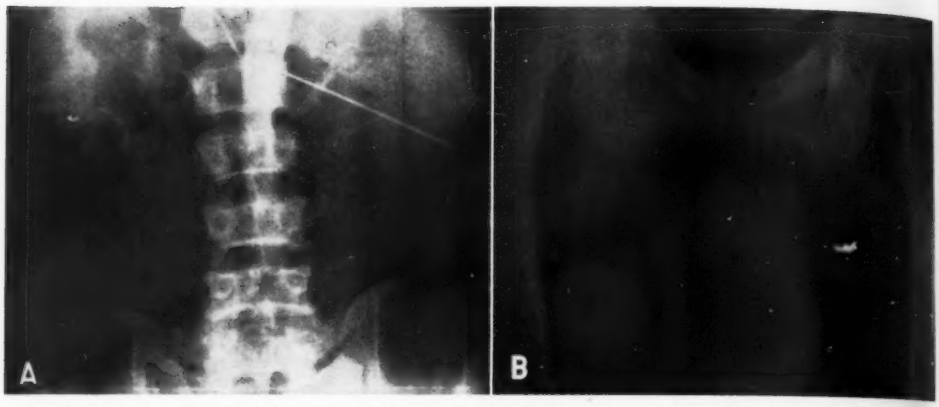

Fig. 5. A. A suprarenal injection with the exposure made just prior to propulsion of the patient. B. This film is the third in the propulsion series. Opacification is too poor in even the upper thighs to employ this injection position with this procedure.

injected. The table speed is preset at a travel rate of 2 inches per second; therefore, the patient moves 6 inches between exposures. Since our film exposure area is 12 inches in length, each succeeding frame incorporates 6 inches of that portion of the body registered on the preceding film. At the time the third film is exposed the upper thigh area is generally under the tube; at this time the injection has just been completed. The cephalad propulsion of the patient is continued until the ankles are under the x-ray tube. The motion of the table is now reversed, and travel continues until the lower abdomen is again under the tube. The average number of exposures is 13.

In Figure 4, A-G, the sequential films obtained from abdomen to ankle are reproduced, while Figure 4, H-I, shows films obtained in reverse propulsion with the tail of the opaque column in the knee areas.

DISCUSSION

Along with other modifications (9), the development and application of this patient-propulsion procedure by the addition of several simple and inexpensive devices has increased the versatility of the main apparatus in the vascular section of our department. It has also been shown that specially designed or manufactured separate units for aorto-arteriography are not essential in our practice; that the apparatus described above is an adequate substitute. Indeed, a method of this type produces studies encompassing greater vascular lengths than does presently marketed apparatus. Actually, most aorto-arteriography, up to the present, has been accomplished and is directed toward visualization of the aorta and great vessels down to an area just beneath the knee. Initially, the capacity to visualize the distal tibial areas seemed to be simply a static addition of further arterial lengths, a by-product that would enable anatomic description of the vessels. Clearly emerging now is the significant amount of added physiological data obtained about patients with high occlusive disease. This gain arises from the opportunity afforded to analyze the distal run-off of the contrast agent. Since delayed and known timing of exposures is practically unrestricted, the flow-time in one extremity may be compared with that in the other. Compilation of flow-time data from numbers of patients permits better understanding of the pathophysiology of the circulation of any one.

It is considered distinctly preferable to inject the opaque bolus below the level of the renal arteries. In the earlier trials, some injections were made above their positions. However, since the injection

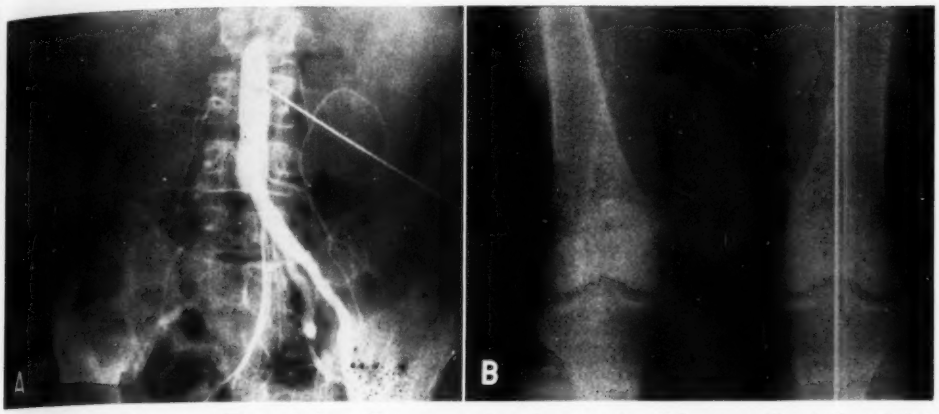

Fig. 6. A. Right common iliac occlusion. Exposure made at five seconds. Subsequent films indicated that the occlusion on the right extended only to the origin of the superficial femoral artery. Despite the complete right iliac occlusion, the time at which the popliteal trifurcations were reached is almost comparable bilaterally at twenty seconds. Films up to twenty-eight seconds showed no filling of the right tibial arteries.

B. During reverse propulsion (thirty-two seconds), opaque medium has completely cleared the left arterial system but not the right superficial femoral artery because of the tibial occlusions. (Refer to text for comment).

time is so prolonged, the loss of the opaque medium in the celiac axis and in the renal arteries appreciably reduced the contrast that was obtained even in the proximal portions of the femoral arteries. This inadequate visualization is shown in Figure 5, A and B.

In reference to the length of time during which the medium is introduced, it is considered that in most cases ten seconds is preferable to fifteen seconds. The ten-second injection time produces a more concentrated bolus and a sufficiently long opaque column to serve the purpose of combined aortic and arterial visualization. A volume of 40 c.c. of medium injected in ten seconds is sufficiently large to have in effect "replaced" the blood in the greater extent of the system. It should be recalled that movement of the patient does not start until half the volume of opaque medium has been injected. This partially insures that the table speed does not outstrip the column of contrast agent.

Some comment is warranted about the speed at which the patient is moved over the film changer. With 3 inches each second, the rate originally used, it was found that too frequently in occlusive disease the arterial flow was less rapid than the rate of motion of the patient. The present table speed of 2 inches per second gives further assurance that the exposure is made of segments of opacified vessels. Films obtained every three seconds give an overlap of approximately 6 inches of the vascular bed on any two of them. This permits one to observe a segment of the vessel twice during the initial phase of cephalad propulsion. Of course, when the patient is returned during reverse movement, the vessel may be visualized a third time at a distinctly delayed interval, in instances of poor flow.

It should be stated that, although there are many advantages to aortic injection and bilateral femoral arterial visualization, there are cases in which direct femoral artery puncture will be mandatory. When occlusive disease is severe within the pelvic vessels, the actual status of the limb arteries may not be determined because of the small amounts of opaque substance reaching them if collateral circulation is poor.

The need for delayed filming as obtained during the reverse propulsion stage is impressed upon one studying surgically created occlusions. In one of our patients with a unilateral mid-thigh amputation, arterial opacified blood was sludged in the

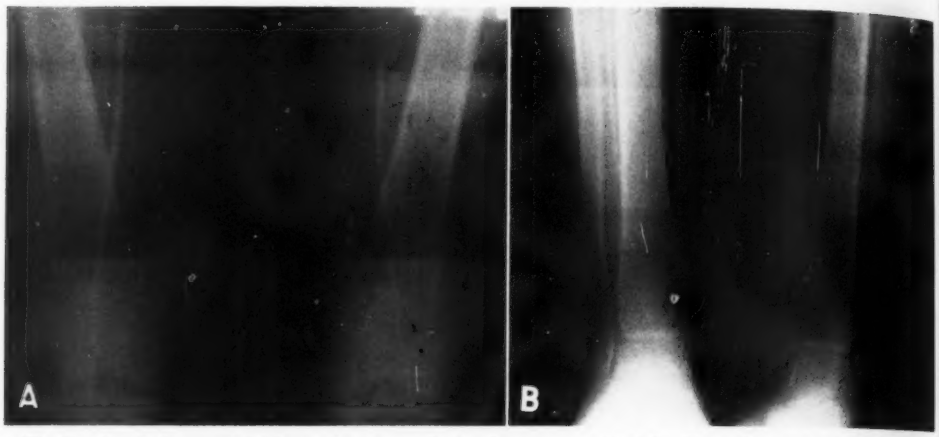

Fig. 7. A. Left superficial femoral artery occlusion (seventeen seconds). Preceding serialographic films had shown the occluded segment to be 8 cm. in length.

B. Reverse propulsion film at twenty-nine seconds, demonstrating distal tibial vessels. Persistence of visualization of the opaque medium bilaterally at this interval indicates that the major vascular problem is in the small vessels of *both* distal legs.

proximal portion of the femoral artery at least twenty-seven seconds after injection. Information, therefore, about run-off blood in a vascular study is considered to be a very important factor. We cannot conclude that either the demonstration of an occlusion or the collateral circulation in the immediate area of the occlusion is totally informative.

For instance, in Figure 6, A, one can note severe occlusive disease of the right common iliac artery. The exposure was made at five seconds following the beginning of introduction of the bolus. Subsequent films indicated that the occlusion on the right extended only to the origin of the superficial femoral artery. The collateral circulation, however, on this right side was sufficiently adequate that the appearance time (twenty seconds) for the bolus was only slightly prolonged in contrast to the flow in the nonoccluded left system at the level of the popliteal trifurcations. Further exposures made up to twenty-eight seconds failed to show filling of the right tibial arteries. That these occlusions were real was substantiated during reverse propulsion (Fig. 6, B) when, at thirty-two seconds, the opaque medium had completely cleared the left arterial system but remained in the right popliteal artery. The presence of the opaque medium in this section is not primarily due to slow transit through the thigh collateral vessels but is also due to occlusive disease in the small vessels of the leg. Had the tibial areas not been visualized, or had delayed timing of exposures not been obtained, one might have concluded that the opaque medium in the popliteal artery was not simply standing there but had merely reached there at a late time because of the higher occlusive change. This case illustrates that, even though the smaller arteries of the distal leg or the collateral arteries of the leg are not demonstrated, conclusions can be drawn concerning circulation because of the time sequencing of the method.

Interestingly enough, in some patients with a high unilateral superficial femoral artery occlusion, one may note that the run-off of blood is as good on the involved side as on the contralateral side. In Figure 7, A there is shown a left superficial femoral artery occlusion ending in the mid-thigh region. This occlusion on previous exposures was seen to be 8 cm. in length. That flow in this extremity is slow is shown in Figure 7, B, obtained at twenty-nine seconds (reverse propulsion phase). However, the opaque medium remains in

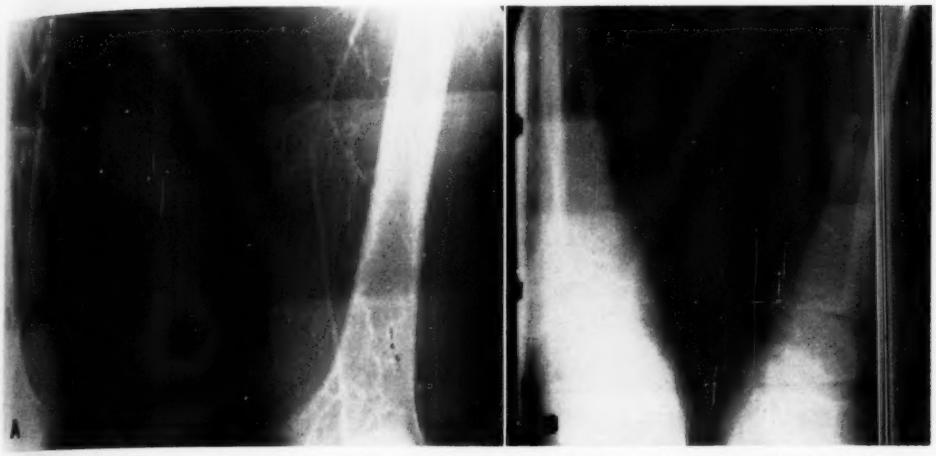

Fig. 8. A. Film demonstrating collateral filling of distal portions of the superficial femoral arteries (fourteen seconds). Segmental occlusions began at the orifices of these arteries.
B. At twenty-three seconds, excellent bilateral tibial run-off is demonstrated. Compare with Fig. 6.

both distal tibial regions. The only explanation that can be offered is that this pooling is due to occlusions in the very small arteries of the ankles and possibly the feet. A comparison of the calf vessels indicates that the opaque medium flow is as far on the left as on the right, despite the left superficial femoral artery occlusion.

These illustrations should be contrasted with those of still another patient; they will emphasize the need for knowledge concerning the more peripheral components of lower extremity circulation. Figure 8, A demonstrates a fourteen-second exposure in the serialographic run. Occlusions in the superficial femoral arteries bilaterally are demonstrated. Earlier exposures had indicated that the thrombotic disease began bilaterally at their orifices. In Figure 8, B, at twenty-three seconds, despite the obliterative disease proximally, the vessels in the ankle areas are seen to be carrying good quantities of the opaque medium. The run-off is excellent bilaterally. One may conclude that reparative surgery in the superficial femoral artery areas may well be expected to be quite effective. Our experience to date in the follow-up of patients is not sufficient for us to imply that surgery should not be carried out in the preceding patient with poor tibial arterial circulation.

Finally, delayed filming through the reverse propulsion technic can be shown to have another advantage. When circulation time in the extremities is slow, false evidence as to the position of actual occlusions may be derived from a single exposure or even from multiple exposures if made too early. In Figure 9, A, bilateral superficial femoral artery thromboses are demonstrated on the eight-second film. In the next illustrated exposure, at fourteen seconds (Fig. 9, B), it is seen that the distal portion of the right superficial femoral artery is filling *via* collaterals down to the very proximal portion of the popliteal segment. This segment is not filled at all on the left. Figure 9, C is a reverse propulsion film obtained at twenty-six seconds; one notes that the popliteal arteries are intact bilaterally.

It might be argued that there is no present requirement to visualize the tibial vessels because vascular surgery has not yet advanced to the stage where repair of such small arteries can be carried out. It is not inconceivable, however, that in the near future methods for small arterial repair will be introduced. But, regardless of the status of small-artery surgery, these studies seem sufficiently convincing if only in the matter of circulation timing

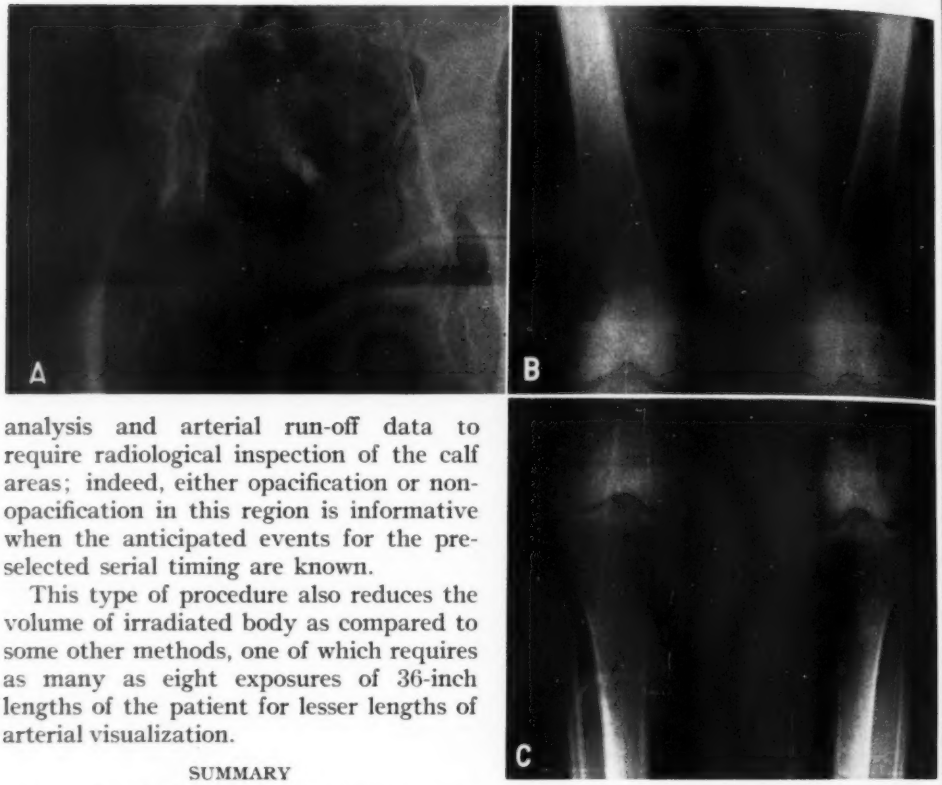

Fig. 9. A. Bilateral superficial femoral artery occlusions (eight seconds).

B. Exposure made at fourteen seconds, demonstrating distal right superficial femoral artery filling via collaterals down to the proximal popliteal artery. This segment is not filled on the left.

C. Reverse propulsion film obtained at twenty-six seconds. The popliteal arteries are filled bilaterally.

analysis and arterial run-off data to require radiological inspection of the calf areas; indeed, either opacification or non-opacification in this region is informative when the anticipated events for the pre-selected serial timing are known.

This type of procedure also reduces the volume of irradiated body as compared to some other methods, one of which requires as many as eight exposures of 36-inch lengths of the patient for lesser lengths of arterial visualization.

SUMMARY

A method for aorto-arteriography in continuity is described. The procedure is based upon propulsion of the patient by means of a motor-driven table over the film-recording area of a serialographic changer. It permits visualization of the arterial system from the region just beneath the renal arteries to the ankles. The reverse propulsion of the patient provides an opportunity to study delayed filling of the vascular bed. The procedure allows opportunities to study circulation flow based on known time-sequencing of the films. It permits analysis of the run-off of the arterial tree so that more adequate judgment can be made concerning repair of more proximal regions of segmental occlusion. The method is simple; it expands the usefulness of serialographic equipment; it is not only a substitute for expensive specialized equipment but allows inspection of even greater arterial lengths.

ACKNOWLEDGMENT: We are indebted to the Winthrop Laboratories for providing the 75 per cent sodium diatrizoate.

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REFERENCES

1. DOS SANTOS, R., LAMAS, A. C., AND CALDAS, J. P.: Artériographie des membres et de l'aorte abdominale. Paris, Masson & Cie, 1931.

2. EYLER, W. R.: Lumbar and Peripheral Arteriography; Technics and Radiologic Anatomy. Radiology **69**: 165–176, August 1957.

3. KINCAID, O. W.: Translumbar Aortography. South. M. J. **51**: 455–464, April 1958.

4. ROGOFF, S. M.: Technique of Serial Long Film Angiography in Arteriosclerosis Obliterans. Am. J. Roentgenol. **76**: 787–800, October 1956.

5. MENENDEZ, C. V., AND LINTON, R. R.: A Technique of Abdominal Aortography and Femoral Arteriography. Surgery **40**: 718–736, October 1956.

6. MORTON, S. A., AND BYRNE, R. W.: Scanographic Methods in Visualization of the Blood Vessels and Skeleton. Radiology **69**: 63–69, July 1957.

7. CHRISTMANN, F. E., AND GRINFELD, D.: Simultaneous Arteriography of the Abdominal Aorta and of the Arteries of the Lower Extremities. Angiology **5**: 339–352, August 1954.

8. ELLZEY, R. F.: A Serial and Chronographic Method of Aortography and Bilateral Arteriography of the Lower Extremities. Radiology **70**: 551–556, April 1958.

9. WIGH, R.: On Increasing the Versatility of Specialized Equipment. Radiology **74**: 77–78, January 1960.

SUMMARIO IN INTERLINGUA

Un Technica de Propulsion del Patiente pro Aorto-Arteriographia

Es describite un methodo pro aorto-arteriographia in continuitate. Le methodo se basa super le propulsion del patiente, per medio de un tabula moto-impellite, super le area del pelliculas de un excambiator serialographic. Illo rende possibile le visualisation del systema arterial ab le region de justo infra le arterias renal usque ad le region del cavilias. Le propulsion revertite del patiente provide un opportunitate de studiar le retardate replenation del vasculatura. Le technica permitte studiar le fluxo circulatori a base de un cognoscite sequentia temporal del pelliculas. Illo permitte le analyse del fluxo ab le vasculatura arterial de maniera que un plus adequate judicamento pote esser formulate in re le reparo de plus proximal regiones del occlusion segmental. Le methodo es simple. Illo augmenta le utilitate del equipamento serialographic. Illo es non solmente un substituto pro apparaturas specialisate sed permitte le inspection de plus grande longores arterial.

Quantitative Relationships Between Radiation Dose and the Reproductive Capacity of Tumor Cells in a Mammalian System In Vivo[1]

ROGER J. BERRY, M.D., and J. ROBERT ANDREWS, M.D.

THE ABILITY TO grow mammalian cells in clonal culture provided the first direct method for measuring the destruction of the reproductive capacity of the cell by ionizing radiation (1). The first system for similarly studying the reproductive capacity of tumor cells in the intact mammalian host was provided by the elegant work of Hewitt and Wilson (2–5). By dividing the number of tumor cells from unirradiated leukemic donor mice necessary to produce tumor "takes" in 50 per cent of recipient mice of the same strain, by the number of tumor cells from irradiated donor animals needed to produce similar 50 per cent "takes," they obtained the "surviving fraction," *i.e.*, the percentage of cells remaining capable of unlimited reproduction after a given dose of radiation. The results reported by Hewitt and Wilson were in close agreement with those obtained *in vitro* and suggested that the reproductive integrity of many mammalian cells, regardless of species, and of normal or malignant origin, showed strikingly similar radiosensitivities. The methods used, however, provided considerable technical difficulty. The isolation of leukemic cells from the livers of donor animals and their accurate recognition (as compared to debris and normal tissue elements) and counting by phase-microscopy were tedious and required considerable skill and experience.

At the National Cancer Institute, we have been most fortunate in having the ascites form of a lymphocytic leukemia in the DBA mouse strain, which lent itself admirably to studies of reproductive capacity and allowed much simpler manipulation. In this communication we shall outline the system used and present the dose-response to x-rays thus obtained under oxygenated and anoxic conditions and with single and fractionated doses.

MATERIALS AND METHODS

Mice: All mice used in this study were females of the DBA/2JN strain, supplied by the animal breeding service of the National Institutes of Health and were the products of brother-sister mating. They were three months old at the start of each experiment.

Tumor: The P-388 lymphocytic leukemia was obtained from Dr. M. Potter, National Cancer Institute, at the 143d generation, having been carried by routine serial passage at weekly intervals in this laboratory over that period. The tumor produces copious, virtually bloodless ascites containing approximately 10^8 tumor cells per milliliter on the seventh day. The experiments reported in this communication encompass generations 245 to 270, but no change in either the character of the tumor or in mean time elapsed between inoculation and death has been noted at any time.

The tumor suspension for routine passage was prepared as follows: The abdomen of a seven-day tumor-bearing mouse was cleansed with 70 per cent alcohol, and under sterile conditions 1–1.5 ml. of ascitic fluid was withdrawn by syringe and immediately diluted with an equal volume of ice-cold Tyrode's solution. A 1:80 dilution of this suspension was made for counting by phase microscopy (although one of the simpler white blood cell counting methods would have sufficed). The characteristic round cells with bright halos

[1] From the Radiation Branch, National Cancer Institute, National Institutes of Health, Public Health Service, Dept. of Health, Education, and Welfare, Bethesda 14, Md. Presented at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, Dec. 4–9, 1960.

under the phase microscope were considered to be morphologically intact tumor cells and numbered over 90 per cent of the total cells counted in every experiment, thus minimizing possible counting error due to mistaken cell identification. The cell suspension was diluted with sufficient ice-cold Tyrode's solution to reach a concentration of 10^7 cells/ml. and 0.1 ml. was injected intraperitoneally into groups of mice numbering 6 to 8 each.

Titration of Leukemia Cells: Serial two- to fourfold dilutions of counted tumor cell-Tyrode suspensions were prepared as above, and 0.1 ml. aliquots of each of a series of four to six such dilutions were injected intraperitoneally into groups of five or six mice. The mean number of leukemic cells injected into any group was calculated by multiplying the cell count for the initial suspension by the dilution factor. The animals were then observed for forty days and the number dying per group was recorded. All animals that died within the forty-day experimental period were inspected for gross signs of leukemia and those dying from other causes were excluded from the data. No leukemias have been seen to develop after the fortieth day, and in several experiments the animals have been continuously observed up to one hundred and twenty days. From the mortality data, the number of cells required to produce leukemia "takes" in 50 per cent of a group of injected recipient mice (the TD50) was calculated by the accumulation method of Reed and Muench (6). The range in numbers of tumor cells injected in any experiment was selected on the basis of the predicted TD50, and every experimental titration included groups with 0 per cent mortality and others with 100 per cent mortality.

Attempted Cell-Free Transfer: (*a*) Seitz-filtrate: The ascitic fluid, diluted 1:1 with ice-cold Tyrode's solution, was immediately passed through a Seitz bacterial filter and 0.1 to 0.2 ml. of the filtrate was injected without further dilution into groups of young mice.

(*b*) Centrifuged supernate: The ascitic fluid, diluted 1:1 as above, was ground briefly in a glass tissue homogenizer and immediately spun at 3,000 RPM for twenty minutes. The supernate was removed by Pasteur pipette and re-centrifuged at 3,000 RPM for twenty minutes; 0.1–0.2 ml. of the supernate from the second spinning was injected without further dilution into groups of young mice.

(*c*) Fluid from irradiated mice: Immediately prior to withdrawal of the ascitic fluid, the donor mouse was exposed to 10,000 rads total-body irradiation. The fluid was withdrawn and diluted appropriately with Tyrode's solution and 0.1 ml. containing 10^6 or 10^7 morphologically intact tumor cells was injected, respectively, into two groups of young mice.

Irradiation: X-rays were generated in the gold target of a Van de Graaff generator operating at 3 Mev. Tumor-bearing animals received total-body irradiation through the back at 50 to 100 cm. target-skin distance, the dose inhomogeneity through the abdomen being less than 10 per cent. The h.v.l. was 10.4 mm. Pb, and the dose-rate 800 to 3,200 rads/min.

RESULTS

The mean survival following intraperitoneal inoculation of various numbers of leukemic cells is shown in Figure 1. Assuming that a similar final number of tumor cells is required to kill the animals in all groups, a tumor-doubling time of approximately fifteen hours can be inferred.

The TD50 for leukemic cells from unirradiated donor animals ranged from 1.5 to 3.5 and averaged 2.3 in 16 experiments. The TD50 was not lowered by inoculation of 1 to 4 viable cells in the presence of 10^6 radiation-killed cells or by pre-inoculation of recipient mice with 10^6 radiation-killed cells. This may be regarded as evidence that there is no significant immune incompatibility between tumor and host. All attempts at transfer by the cell-free preparations described failed to produce tumors up to three months subsequent to inocula-

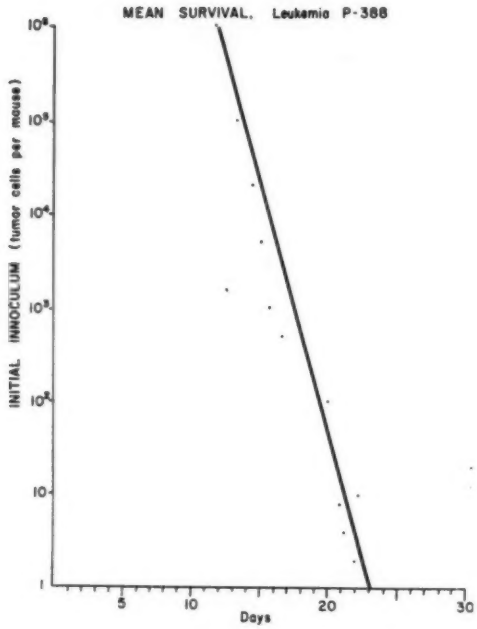

Fig. 1. Mean survival of recipient animals following inoculation of various numbers of leukemia P-388 cells.

tion. Thus, tumor induction by virus or other agent can be discarded as a significant factor in these relatively short-term experiments.

Dose-Response Curve: Tumor-bearing donor animals were subjected to a single dose of total-body irradiation immediately prior to aspiration of the ascitic fluid. The "surviving fraction" (*i.e.*, cells remaining capable of reproduction) after irradiation is defined as Control TD50/Irradiated TD50 and is a function of x-ray dose, as shown in Figure 2. No difference was noted between results in experiments in which the animals were breathing air or 100 per cent oxygen at the time of irradiation and those in which the donor animal had been killed ten to twenty minutes prior to irradiation. Results under all these conditions therefore signify the *anoxic* radiosensitivity of reproductive capacity of P-388 leukemic cells. Each point represents the mean of at least two separate experiments; the regression line was determined by the method of least squares and the slope of the straight portion indicates a mean lethal dose (D_0) of 365 rads and an extrapolation number of 1.6 under these anoxic conditions.

In order to provide thorough oxygenation of the ascites tumor, 3 per cent hydrogen peroxide was injected intraperitoneally, to a final concentration of 0.2 *M* in the ascitic fluid prior to irradiation. This procedure did not raise the TD50 of unirradiated cells in six replicate experiments, but the liberation of oxygen bubbles by the action of catalase in the tumor fluid provided adequate oxygenation for the tumor cells during irradiation. The dose-response curve under these conditions of oxygenation is also shown in Figure 2: its slope differs from the anoxic curve by a factor of 2.3:1, with a D_0 of 160 rads and an extrapolation number similar to that of the anoxic curve.

Dose Fractionation: To compare the effects of single-dose irradiation with effects of the same total dose delivered in fractions, tumor-bearing donor animals were given one to four daily total-body exposures of 500 rads. The final dose was delivered immediately prior to aspiration of ascitic fluid and titration into recipient animals. Results are shown in Figure 3. As the number of fractions is increased, the recovery of sublethally irradiated cells with time becomes apparent, and the efficiency of the total dose in "sterilizing" tumor cells decreases. No increase in the percentage of morphologically damaged cells was noted in the cell suspensions from animals which had received fractionated doses, and the concentration of leukemic cells per milliliter of tumor fluid was significantly lowered only in the 4 × 500 rad group.

DISCUSSION

The transplantable murine leukemia described in this communication offers an *in vivo* system with many of the advantages of *in vitro* tissue culture systems for radiobiologic study. The repeatably low TD50 for cells from unirradiated donors and the inability to alter this TD50 value either by giving small numbers of viable tumor cells in the presence of large numbers of radia-

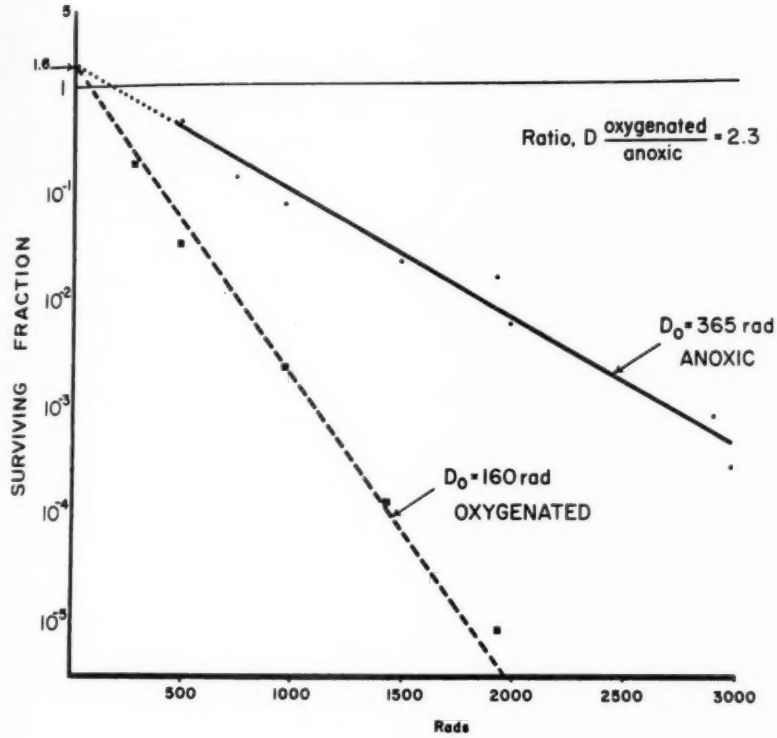

Fig. 2. Dose response, 3 Mev x-rays. Leukemia P-388.

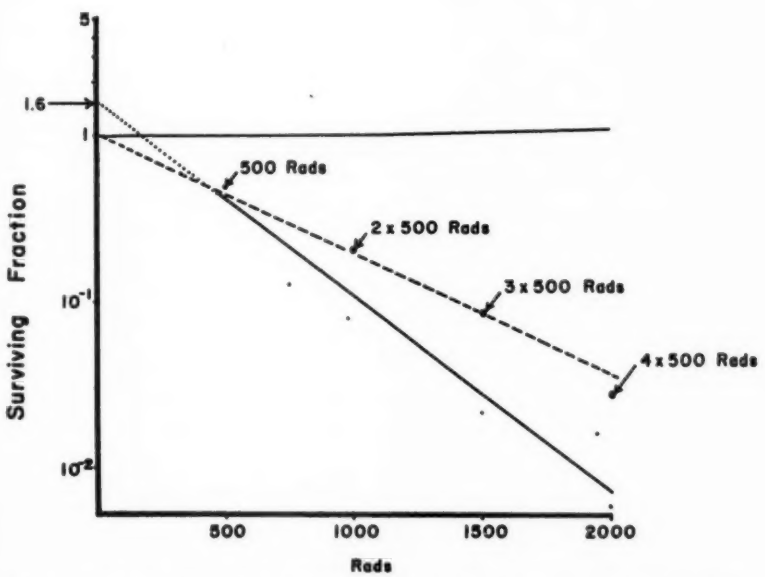

Fig. 3. Dose fractionation, 3 Mev x-rays, leukemia P-388. Solid line, single-dose irradiation. Broken line, fractionated dose, 500 rads daily increments.

tion-killed cells or by pretreatment with large numbers of radiation-killed cells satisfy the Revesz criteria for absence of immune incompatibility between tumor and host (7). The P-388 leukemia has been maintained in females of the closely inbred strain in which it arose and has shown remarkable genetic constancy through 270 serial passages. This is probably due in part to rigid standardization of the routine transplantation regimen. The tumor has never been known to regress spontaneously and kills recipient animals with clock-like regularity twelve days after intraperitoneal inoculation with 10^6 cells.

The dose-response curve to x-rays shows a majority of the cells to be anoxic even when the animal is breathing 100 per cent oxygen. It is true that the theoretical dose-response curves of Hewitt and Wilson suggest that it would be difficult indeed to detect the presence of a small number of oxygenated cells in the presence of a large predominance of anoxic cells (4), but the tumor volume in the seventh-day mouse is usually 5 to 7 ml., and it is not surprising that at any point in time a majority of cells are more than 145 μ from a blood capillary [the maximum radius of oxygenation in tissue about a blood vessel, according to Thomlinson and Gray (8)]. Although Deschner and Gray were able to influence the oxygen tension in the ascites fluid of a tumor-bearing mouse somewhat by altering the oxygen partial pressure of the inspired gas, they dealt with a total tumor volume of only 2 ml. and could expect better gas exchange with the capillary blood supply (9). Their method of injection of hydrogen peroxide to produce oxygenated conditions did not cause an increase in chromosomal damage in unirradiated tumors at 0.1 *M* concentration; similarly a 0.2 *M* concentration of hydrogen peroxide failed to increase the TD50 for tumor cells from unirradiated donor animals in the system reported here. The dose-response curves for P-388 leukemic cells under anoxic and oxygenated conditions agree remarkably well with the observations of Hewitt and Wilson upon murine leukemic cells derived from the liver, and with the *in vitro* observations of Puck *et al.* in several lines of normal and malignant human and hamster-derived cells, when corrected for errors in measurement of absorbed x-ray dose (10). Until and unless there is evidence of mammalian cells whose radiosensitivity is widely different from the values reported here, the mean lethal dose of 160 rads under oxygenated conditions may be used as a reasonable starting point in an attempt to rationalize radiation doses necessary to "cure" (*i.e.* sterilize) tumors of various sizes.

The data obtained following fractionated irradiation suggest that the demonstration of the recovery of sublethally irradiated cells *in vitro* by Elkind (11) has been confirmed here *in vivo*. In addition, the decreased efficiency of multiple fractions may be independent of oxygen tension, as the results reported in this communication were obtained in an anoxic system, while Elkind reported on fully oxygenated cells. While cell death in tumors receiving fractionated irradiation cannot be ruled out, the failure to find an increase in the number of morphologically damaged cells and the maintenance of normal tumor concentration (cells/ml.) up to four fractionated doses add support to the surmise that this is, in fact, a demonstration of cell recovery. Further studies of the kinetics of the irradiated tumor population are needed, however. The implications of cell recovery in radiotherapy have recently received extensive theoretical consideration by Lajtha, Oliver, and Ellis (12, 13); the results reported here are another indication that it is necessary, when calculating the percentage of tumor cells likely to be destroyed by a projected course of radiotherapy, to include allowance for cells recovering in the interval between treatments.

The usefulness of the system described in this communication, however, is that it provides a method for studying the comparative effects of radiations of different ionization density (LET) and a workable *in vivo* method for studying the combined effects of irradiation and chemotherapeutic

agents upon reproductive capacity of tumor cells. Studies of the use of halogenated pyrimidine deoxyribosides (halogenated DNA precursor-analogues) plus irradiation are in progress and will be reported separately.

SUMMARY

A quantitative system for the determination of relationships between radiation dose and the reproductive capacity of tumor cells has been developed with use of the ascites form of a transplantable mouse lymphocytic leukemia. The system offers freedom from host-immunity factors and provides a method for studying changes in radiosensitivity related to alteration in oxygen tension, ionization density of the radiation (LET), or as induced by pharmacological agents. The method is important because it permits the study of these effects and of dose fractionation in the intact mammal rather than in free cell culture or simpler biological systems. Application to radiotherapy is discussed.

ACKNOWLEDGMENT: Thanks are due to Dr. Harold B. Hewitt, Westminster Hospital, London, England, for advice and encouragement, and to Miss Marion Matthews and Mr. Bruce Weed for invaluable technical assistance.

REFERENCES

1. PUCK, T. T., MORKOVIN, D., MARCUS, P. I., AND CIECIURA, S. J.: Action of X-Rays on Mammalian Cells. II. Survival Curves of Cells from Normal Human Tissues. J. Exper. Med. **106**: 485–500, October 1957.

2. HEWITT, H. B.: Studies of the Dissemination and Quantitative Transplantation of a Lymphocytic Leukaemia of CBA Mice. Brit. J. Cancer **12**: 378–401, September 1958.

3. HEWITT, H. B., AND WILSON, C. W.: A Survival Curve for Mammalian Leukaemia Cells Irradiated *In Vivo* (Implications for the Treatment of Mouse Leukaemia by Whole-Body Irradiation). Brit. J. Cancer **13**: 69–75, March 1959.

4. HEWITT, H. B., AND WILSON, C. W.: Effect of Tissue Oxygen Tension on Radiosensitivity of Leukaemia Cells Irradiated in Situ in Livers of Leukaemic Mice. Brit. J. Cancer **13**: 675–684, December 1959.

5. HEWITT, H. B., AND WILSON, C. W.: Further Studies Relating to the Implications of Radiation Survival Curve Data for Treatment of CBA Mouse Leukaemia by Whole-Body Irradiation. Brit. J. Cancer **14**: 186–194, June 1960.

6. REED, L. J., AND MUENCH, H.: A Simple Method for Estimating Fifty Per Cent Endpoints. Am. J. Hyg. **27**: 493–497, May 1938.

7. REVESZ, L.: Detection of Antigenic Differences in Isologous Host-Tumor Systems by Pretreatment with Heavily Irradiated Tumor Cells. Cancer Res. **20**: 443–451, May 1960.

8. THOMLINSON, R. H., AND GRAY, L. H.: Histological Structure of Some Human Lung Cancers and Possible Implications for Radiotherapy. Brit. J. Cancer **9**: 539–549, December 1955.

9. DESCHNER, E. E., AND GRAY, L. H.: Influence of Oxygen Tension on X-Ray-Induced Chromosomal Damage in Ehrlich Ascites Tumor Cells Irradiated In Vitro and In Vivo. Radiation Res. **11**: 115–146, July 1959.

10. MORKOVIN, D., AND FELDMAN, A.: Dosimetry in Living Cells Irradiated on Glass. A Correction. Brit. J. Radiol. **32**: 282, April 1959.

11. ELKIND, M. M.: Cellular Aspects of Tumor Therapy. Radiology **74**: 529–540, April 1960.

12. LAJTHA, L. G., OLIVER, R., AND ELLIS, F.: Rationalisation of Fractionation in Radiotherapy. Brit. J. Radiol. **33**: 634–635, October 1960.

13. LAJTHA, L. G., AND OLIVER, R.: Some Radiobiological Considerations in Radiotherapy. Brit. J. Radiol. **34**: 252–257, April 1961.

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DISCUSSION

Henry Kaplan, M.D. (Palo Alto, Calif.): The system just described is of interest and I don't mean my remarks in any way to cast aspersions on its usefulness in the pursuit of further investigations. However, I believe that certain statements made about the system need not be correct in order to make it of interest. First of all it was stated that there is no evidence for viral etiology of this leukemia simply because filtrates made from the leukemic cells failed to elicit leukemia—I presume in adult mice injected with the filtrates. This is, of course, quite unacceptable evidence. Anyone who has worked with viral passage of leukemia in mice knows what an exceedingly tricky and difficult job this is, even when one uses newborn, highly susceptible mice. The capriciousness with which one may or may not find viral activity in different experiments should cause us to exercise a great deal of caution as to whether there is a virus present. I repeat, it really doesn't matter one iota whether there is a virus present or not; the data are of interest no matter what the etiology of the tumor.

Secondly, the statement is made that this leukemia has no immunologic reactivity with the host. I wondered whether the tests conducted to examine this point were adequate to make that statement? If you refer to a paper given by Dr. Oliver Scott at last year's Radiation Research Society meeting, you will find that highly stringent tests are essential to determine immunologic differences. I wonder if the essayists used large doses of radiation-killed leukemic cells injected into hosts three or four times prior to challenge with live unirradiated leukemic cells? Under those conditions if the TD50 were still the same

I think they would then have a basis for this statement.

Dr. Berry (*closing*): As to Dr. Kaplan's first point, my only reason for saying that we have no evidence of a viral agent at work is that we used not only the filtrates, but also additional cells that were broken and centrifuged (not ultra-centrifuged) at 3,000 RPM for twenty minutes. This is undiluted tumor fluid, a concentration ten thousand times that normally used when transplanting one cell. This has failed to produce tumors in both adult and newborn mice.

In addition, we have taken the cells from donor animals irradiated with 10,000 rads, which is a dose which would not be expected to affect viruses but on the other hand is sufficient to kill all the cell population. We have injected this into both adult and newborn mice and, although the tumor kills our animals in less than forty days, we have now gone over four months and see no evidence of tumor in any of these animals.

In answer to the second point, we used multiple challenges, one or two challenges with one million killed cells, prior to using viable cells and we saw no change in the TD50. The donor was irradiated with 10,000 rads.

SUMMARIO IN INTERLINGUA

Relationes Quantitative Inter le Dose de Radiation e le Capacitate Reproductori de Cellulas Tumoral in un Systema Mammalian in Vivo

Un systema quantitative pro le determination del relationes inter le dose de radiation e le capacitate reproductori de cellulas tumoral ha essite disveloppate con le uso del forma ascitic de un transplantabile leucemia lymphocytic murin. Le systema es libere del effecto de factores de immunitate del parte del hospite e provide un methodo pro studiar alterationes del radiosensibilitate in tanto que illos es relationate con alterationes in le tension de oxygeno o in le densitate de ionisation del radiation o in tanto que illos es inducite per le action de agentes pharmacologic. Le methodo permitte le studio de iste effectos e del fractionation del dosage in le intacte mammal plus tosto que in un cultura de cellulas libere o in un plus simple systema biologic. Applicationes in le radiotherapia es discutite.

Le resultatos del hic-reportate studios indica le necessitate—in calcular qual procentage del cellulas tumoral va probabilemente esser destruite per un projicite curso de radiotherapia—de includer le factor que un certe quantitate de cellulas se restabli durante le intervallo inter le tractamentos.

A Disposable Kit for Barium Enemas[1]

RUBEM POCHACZEVSKY, M.D., ROBERT S. SHERMAN, M.D., and PHILLIP H. MEYERS, M.D.

THE PRESENT methods of preparation and administration of the barium sulfate mixture in roentgen examination of the large bowel have certain disadvantages. The equipment, consisting of enema can, tubing, tip, and air-insufflation apparatus, must be carefully cleaned and sterilized. Sterilization, especially of the apparatus for air insufflation, is indeed difficult and is often neglected. Furthermore, measuring and mechanical mixing of the barium sulfate and water, whether done individually for each patient or carried out in a single, larger effort, consume additional time, with the possibility of variations in the consistency of the mixture unless great care is exercised. Settling of the mixture before and even during its administration must be guarded against by frequent stirring. The chances of spillage from the can at one time or another are real and seemingly unavoidable.

Considerations such as these prompted one of us (P.H.M.) to devise a disposable, plastic enema kit. The bag measures 14 × 7.5 inches. Being heat-sealed, it is impact-resistant (a 2 1/2-quart bag dropped 8 feet will not burst). It is provided with an upper spout for the addition of water (Fig. 1). Another special feature is the outlet tube extending inside the bag for 3 inches, with numerous 1/8-inch openings over its surface, which act as a filter, preventing large particles or clumps of barium from entering the tubing. This is important because a homogeneous mixture of barium is necessary for even coating of the colonic mucosa and for the prevention of flocculation, crusting, and similar artefacts.

The bag contains barium sulfate, a suspending agent in predetermined amounts, and tannic acid or not, as preferred. A dependable barium mixture, according to the individual examiner's preference, is therefore readily obtained. There is no need for the storage of large quantities of barium nor for the use of additional personnel to prepare the opaque mixture. After the addition of a set amount of warm water through the upper spout, followed by kneading and squeezing of the bag for less than one minute, the material is ready for use.

Fig. 1. The disposable barium-enema kit.

Since the bag can be used with the upper spout clamped, there is no danger of contamination such as may occur with an open enema can, especially if the contents in a previously contaminated can are mixed too vigorously, with consequent splashing (1).

Another advantage of the plastic bag is that, when filled, an effective control of the barium flow can be obtained by simple manual pressure. Due to the elasticity of the system, pressure gradients are

[1] From the Department of X-ray Diagnosis, Memorial-Sloan Kettering Center for Cancer and Allied Diseases, New York, N. Y. Accepted for publication in May 1961.

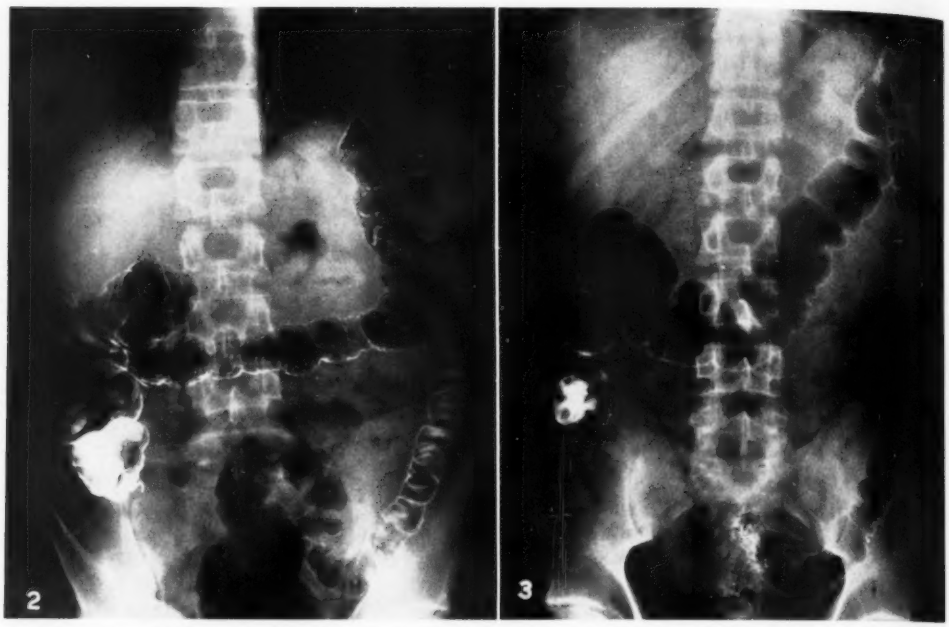

Fig. 2. Unsatisfactory air study in a routine barium-enema examination. Note the presence of crusts and clumps of barium, particularly in the transverse colon, producing disturbing shadows.
Fig. 3. Same patient as in Fig. 2. Smoother coating of the mucosa following use of disposable kit.

flexible and easily and instantly controlled. Gravity flow can be used, however, by leaving the upper spout unclamped and elevating the bag, if this method is preferred. The same bag, after being emptied, can then be used for air insufflation by filling it with air, clamping the upper spout, and gently applying manual pressure under fluoroscopic control.

A particularly useful feature is that the entire enema may be withdrawn into the bag whenever the patient complains of overdistention, cramps, or an uncontrollable urge to evacuate. With conventional equipment the entire system would, of course, be thoroughly contaminated, including the enema can. We have learned that this feature is valuable in reassuring patients that any sense of distention or discomfort can be immediately relieved. Spillage of barium is therefore quite avoidable and should not ordinarily occur.

In offices and small x-ray departments where roentgen examination of the colon is not frequently carried out, the use of the disposable kit is especially advantageous.

Actual contamination by fecal contents of the enema tubing, and even of the can, which is usually located a few feet above the table, can occur in a significant percentage of cases (3, 5). Nathan (4) found intrarectal water pressures above 75 cm. of water with resultant backflow of feces in the enema container in 12 of 14 patients exhibiting mass peristalsis. Controlled bacteriologic studies and experiments employing radioisotopes appear to confirm this (3, 5). The danger seems to increase if the patient performs an involuntary Valsalva type maneuver or when cramps or spasm of the colon occur during the examination. The intrarectal pressure may increase considerably in these circumstances, and during defecation it may be as high as a 9-foot column of water (3, 5). Simple substitution of the enema tips and washing of the tubing and can constitute common practice, but do not necessarily prevent contamination from patient to patient. Sterilization of the entire enema

equipment following each examination is not always feasible or practical, especially in a busy hospital or office practice. When patients with known typhoid fever, shigellosis, infectious hepatitis, amebiasis, poliomyelitis (2), infestations with certain species of worms or parasites, or other diseases due to enteric pathogens are to be examined, a disposable kit seems clearly indicated.

The disposable bag has been tested over a period of several months. In all examinations a satisfactory diagnostic result was obtained and there have been no accidents or difficulties. In many cases, previous barium-enema films were available for comparison. In most instances the study with the kit was as good as and sometimes superior to the earlier one, and in none was a fault encountered which could be attributed either to the device or the medium it contained. The post-evacuation films and the air distention studies were of consistently good quality, sometimes better than in previous examinations (Figs. 2 and 3).

SUMMARY

The authors present their clinical experience with the use of a disposable barium-enema kit. Among its advantages are: prevention of transmission of enteric pathogens from patient to patient; excellent mixture of barium sulfate and water, insuring good diagnostic films; saving in labor and time and increased convenience; low cost, making the kit practical from an economic standpoint.

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REFERENCES

1. DARLOW, H. M., AND BALE, W. R.: Infective Hazards of Water-Closets. Lancet **1:** 1196–1200, June 6, 1959.

2. GELFAND, H. M., POTASH, L., LEBLANC, D. R., AND FOX, J. P.: Intrafamilial and Interfamilial Spread of Living Vaccine Strains of Polioviruses. J.A.M.A. **170:** 2039–2048, Aug. 22, 1959.

3. MEYERS, P. H.: Contamination of Barium Enema Apparatus During Its Use. J.A.M.A. **173:** 1589–1590, Aug. 6, 1960.

4. NATHAN, M. H.: Clinical and Roentgenologic Correlation of Physiology of the Colon. Am. J. Roentgenol. **81:** 650–660, April 1959.

5. STEINBACH, H. L., ROUSSEAU, R., MCCORMACK, K. R., AND JAWETZ, E.: Transmission of Enteric Pathogens by Barium Enemas. J.A.M.A. **174:** 1207–1208, Oct. 29, 1960.

SUMMARIO IN INTERLINGUA

Guarnitura de Clyster a Barium, a Uso Unic

Un guarnitura de clyster a barium, ex plastico a uso unic, esseva elaborate. Su dimensiones es 14 × 7,5 pollices. Illoes thermo-serrate e ha un orificio al extremitate superior pro le infusion de aqua. Le tubo de egresso protrude per 3 pollices al interior del sacco. In ille section del tubo il ha multiple aperturas de un octavo de un pollice que age como filtro pro prevenir le egression de grande particulas o grumos de barium. Le orificio al extremitate superior pote esser crampate pro eliminar le periculo de un contamination. Le mesme sacco, post su vacuation, pote esser usate pro insufflar aere.

Le integre clyster pote esser retrahite ad in le sacco quando le patiente se plange de hyperdistention o de crampos. Altere avantages del uso de iste clyster es: Le prevention del transmission de pathogenos enteric ab un patiente al altere; un excellente miscimento de sulfato de barium con aqua, assecurante le obtention de bon pelliculas diagnostic; economia in travalio e tempore, con manipulationes de alte convenibilitate; e basse costos.

Disposable, Plastic Unit for Barium-Enema Examination[1]

JACK R. DREYFUSS, M.D.,[2] LAURENCE L. ROBBINS, M.D.,[3] and JOHN T. MURPHY, Phm.D.[4]

WHEN ONE CONSIDERS the strict precautions taken in most hospitals and private offices to prevent cross-infection between patients, it seems absurd that so little has been done to make the barium-enema examination safer, if not esthetically more acceptable. The former practice of refilling the same enema can and tubing for successive patients during a morning's fluoroscopic session has not been rendered much less revolting by the ruse of allotting to each patient a freshly autoclaved enema tip or even a disposable plastic one. Anyone who has used clear plastic tubing to connect the enema can and the rectal tip is aware that grossly visible fecal material frequently refluxes from the filling colon well into the tubing and may even reach the enema can. The customary use of a metal can and rubber tubing, hiding this fecal reflux, may have served to keep our consciences clean, but little else.

In two recent articles in the *Journal of the American Medical Association* (1, 2) attention was called to the very real danger of cross-infection as a result of the deposition of bacteria refluxed with the barium mixture from the colon into the tubing and can of the barium-enema apparatus. This occurs particularly when the colon goes into spasm, but it may happen when the patient simply coughs or changes position. Although little documentation of the spread of enteric disease by this method has been published, it may well occur. Certainly, the medieval filth of the present situation requires a more satisfactory technic for barium-enema examination.

For several years we have provided a freshly autoclaved barium-enema can and tube with a disposable plastic rectal tip for each patient. Although this was a vast improvement over apparatus washed in soap and water, it involved a considerable number of cans and many feet of cracked tubing. An inexpensive, completely disposable unit (reservoir, tube, and tip) made of plastic is probably the ideal solution.

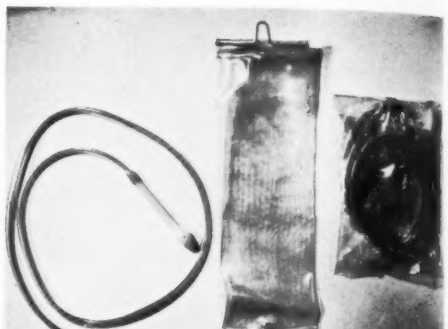

Fig. 1. One-piece disposable plastic enema unit folded within a sealed plastic envelope, on the right, and open, ready for use, on the left.

Increasing dissatisfaction with the existing methods led our Department of Radiology to request such a disposable unit, which was designed for us by the Director of Pharmaceutical Research and Development at the Massachusetts General Hospital and then manufactured by a hospital equipment company[5] in sufficient quantity for a pilot study. The one-piece unit consists of a 1 1/2-quart reservoir, 6 feet of tubing, and a rectal tip. A wire spreader in the top seam of the bag also serves as a hook by which it may be suspended. The entire unit is made of poly-

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[4] Director of Pharmaceutical Research and Development, Massachusetts General Hospital.

[5] The Macbick Company, 243 Broadway, Cambridge 39, Mass.

vinyl chloride and individually packaged in a plastic envelope (Fig. 1). Filling of the colon is controlled by a Kelly clamp. The tubing can easily be cut for the connection of a two-way system for air-contrast examinations or a retention catheter by means of plastic adapters.

Although we recognize the disposable one-piece unit as a real advance in cleanliness and efficiency, there are still two "loop-holes" to be filled before the system is perfect for all types of barium-enema examination. The styles of rubber insufflators now used in performing air-contrast enemas are as susceptible to back-flow contamination as are the old-fashioned rubber tube and metal can system. Similarly, the interposition of a rubber Foley-type catheter for retention of the enema in the colon presents another chance for cross-infection if the unit is not adequately cleaned and sterilized. We have therefore suggested the development of a disposable plastic retention catheter, as well as an air insufflator, which we anticipate will soon be available.

The advantages of a disposable, plastic enema unit should recommend its use not only for barium-enema examinations but for any type of enema administered in a hospital or doctor's office.

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REFERENCES

1. MEYERS, P. H.: Contamination of Barium Enema Apparatus During its Use. J.A.M.A. **173:** 1589–1590, Aug. 6, 1960.
2. STEINBACH, H. L., ROUSSEAU, R., MCCORMACK, K. R., AND JAWETZ, E.: Transmission of Enteric Pathogens by Barium Enemas. J.A.M.A. **174:** 1207–1208, Oct. 29, 1960.

SUMMARIO IN INTERLINGUA

Un Dispositivo de Plastico a Uso Unic pro Examines a Clyster de Barium

Esseva elaborate un clyster de plastico a uso unic, consistente de un reservoir con un capacitate de un quarto e medie, 6 pedes de tubo, e un puncta rectal. Un filo metallic in le sutura al extremitate superior del sacco servi a tener le sacco extendite. Le filo se termina in un ansa, per medio del qual le sacco es suspendite. Le complete guarnitura es facite de chloruro polyvinylic e impaccate individualmente in un enveloppe de plastico. Le influxo ad in le colon es regulate per medio de un crampa Kelly. Le tubo es facile a secar pro establir connexiones in un systema bidirectional in examines a contrasto per aere o pro accomodar un catheter de retention per medio de intermediarios de plastico.

Es opinate que iste dispositivo preveni infectiones cruciate que es causate per le refluxo de feces ab le colon ad in le tubo.

Unusual Appearance of the Colon Following Sigmoid Volvulus[1]

NORMAN L. AVNET, M.D., and MILTON ELKIN, M.D.

THE SIGMOID colon is the most common site of volvulus of the large bowel. The diagnosis is usually made from the clinical findings and roentgen study of the abdomen; barium-enema examination is not, as a rule, necessary. The characteristic radiologic appearance of this closed-loop variety of colonic obstruction has been well documented (5, 6, 12–15). Its mortality rate has been high, and death is frequently associated with gangrene of the involved segment of the sigmoid. The usual treatment is surgical, but rectal intubation with sigmoidoscopy has been recommended for cases without evidence, proctoscopically, of circulatory embarrassment (1). Although there are numerous reports of the aspect of sigmoid volvulus on barium-enema examination, we have come across none on the appearance soon after detorsion of the volvulus.

This is a report of a patient with sigmoid volvulus treated by intubation through a sigmoidoscope. Barium-enema study three days after the detorsion demonstrated striking changes in the sigmoid colon.

CASE REPORT

B. H., a 78-year-old white female, was admitted to the Bronx Municipal Hospital Center on Dec. 1, 1959, with a four-day history of abdominal pain and distention, without vomiting. She had passed no flatus for two days and had only a small bowel movement the day before admission. There was no history of melena or hematemesis. Anorexia had been present for one day.

After admission to the hospital, films of the abdomen demonstrated the typical appearance of sigmoid volvulus (Fig. 1). A sigmoidoscope was passed to 20 cm. where a "constricting mass" was encountered in the bowel. As the instrument was passed through the narrowed area, a large amount of gas and watery stool was evacuated, with subsequent subsidence of the abdominal distention and pain. Three days later a barium-enema examination was performed (Figs. 2–4), demonstrating a wide and redundant loop of sigmoid colon with multiple serrations along its borders, having the appearance of numerous small ulcers. The postevacuation film showed pronounced thickening of the sigmoid mucosa. It was believed that these changes represented mucosal edema and ulceration due to circulatory embarrassment at the time of the volvulus. At sigmoidoscopy two days later, however, the sigmoid exhibited only mild injection of the mucosa with no evidence of ulceration. The patient did well and was discharged on a low residue diet.

One month after the first admission, a similar episode led to an elective resection of a huge redundant loop of dilated sigmoid colon. Gross and microscopic study of the resected specimen showed only minimal signs of venous stasis. There was mild congestion of the subserosal and submucosal venules. A small amount of proteinaceous hyaline-staining material was present in somewhat dilated lymphatics. There was no fibrous change, scarring, or evidence of any ulceration; the glandular portions of the mucosa were normal. Only mild edematous change in the wall was observed.

DISCUSSION

Abdominal films in this case (Fig. 1), at the time of acute obstruction, demonstrated the findings of volvulus of the sigmoid colon as described by Rigler *et al.* (14). Only because the sigmoidoscopist thought he saw a mass at the rectosigmoid junction was a barium-enema examination performed after the first detorsion of the volvulus. The films suggested severe edema with ulceration of the sigmoid mucosa. Sigmoidoscopy two days later, however, showed no ulceration, although there was residual evidence of edema. The mucosal edema was probably due to circulatory embarrassment during the volvulus.

Engelhardt and Jacobson (3), and others (8), have described the appearance on barium-enema examination in infarction of the colon due to inferior mesenteric thrombosis. In the case reported by Engelhardt and Jacobson the bowel was narrowed and rigid, and the mucosa was edematous. Our patient showed similar

[1] From the Department of Radiology, Albert Einstein College of Medicine of Yeshiva University, and Bronx Municipal Hospital Center, New York. Accepted for publication in March 1961.

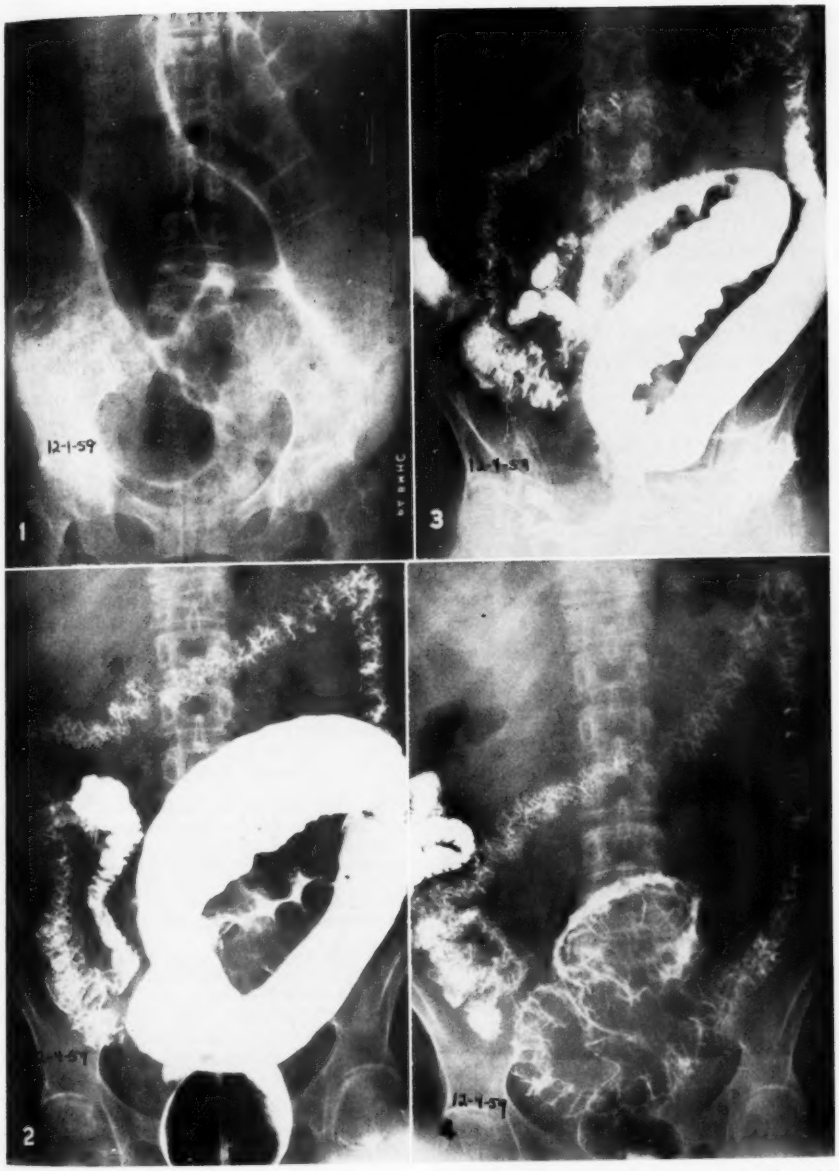

Fig. 1. Initial study of the abdomen. Flat film demonstrating gross dilatation of the sigmoid colon which is now oriented toward the right upper abdominal quadrant. There is also distention of the large bowel proximal to the area of volvulus.

Fig. 2. Barium-enema film three days after reduction, showing multiple small irregularities of the walls of the sigmoid colon, simulating ulcerations.

Fig. 3. Anteroposterior view following partial evacuation. On this film the anatomy is more easily reconstructed and one can see how the redundant loop of sigmoid colon would orient toward the right upper quadrant if it rotated on itself. Note the irregularity of the lumen of the sigmoid, with multiple serrations.

Fig. 4. Evacuation film, showing marked edema of the sigmoid mucosa.

changes, although less severe. Wolf and Marshak (16), in reporting cases of segmental infarction of the small bowel, stated that, of the different layers of the intestine, the mucosa is most sensitive to interference with the blood supply. The mucosa, however, has great powers of regeneration and, in the absence of extensive destruction, there may be restitution to a normal state histologically, without fibrosis.

The impression of the edematous folds on the bowel lumen, in the film obtained after partial evacuation, resembles the changes seen in extensive pneumatosis of the colon recently described by Marshak *et al.* (9) and Creevey *et al.* (2). Frimann-Dahl reported the development of interstitial emphysema in severe sigmoid volvulus (6). The case at hand, however, failed to show gas in these bleb-like indentations on the bowel wall.

SUMMARY

A case is reported in which striking changes were demonstrated in the sigmoid colon on barium-enema study after nonoperative detorsion of sigmoid volvulus. It is suggested that this appearance was due to mucosal edema resulting from embarrassment of the blood supply to the sigmoid during the volvulus. The injury to the mucosa was not extensive, and regeneration occurred without fibrosis.

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REFERENCES

1. BRUUSGAARD, C.: Volvulus of the Sigmoid Colon and Its Treatment. Surgery **22:** 466–478, September 1947.

2. CREEVEY, K., COHEN, J. L., AND RILEY, G. J.: Pneumatosis of the Descending Colon. New England J. Med. **259:** 912–915, Nov. 6, 1958.

3. ENGELHARDT, J. E., AND JACOBSON, G.: Infarction of the Colon Demonstrated by Barium Enema. Radiology **67:** 573–574, October 1956.

4. EPSTEIN, B. S.: Clinical Radiology of Acute Abdominal Disorders. Philadelphia, Lea & Febiger, 1958, pp. 45–49.

5. FIGIEL, L. S., AND FIGIEL, S. J.: Sigmoid Volvulus: Variations in the Roentgen Pattern. Am. J. Roentgenol. **81:** 683–693, April 1959.

6. FRIMANN-DAHL, J.: Roentgen Examination in Acute Abdominal Diseases. Springfield, Ill., Charles C Thomas, 1951, pp. 189–207.

7. KREEGER, N., AND LITTMAN, L.: Pneumatosis Cystoides Intestinorum; Report of Cases Confirmed by Sigmoidoscopic Biopsy. New England J. Med. **251:** 779–781, Nov. 4, 1954.

8. LISTER, E., AND JUNGMANN, H.: Gangrene of the Colon. Brit. J. Radiol. **29:** 341–343, June 1956.

9. MARSHAK, R. H., BLUM, S. D., AND ELIASOPH, J.: Pneumatosis Involving the Left Side of the Colon. J.A.M.A. **161:** 1626–1628, Aug. 25, 1956.

10. MARSHAK, R. H., LIPSAY, J. J., AND FRIEDMAN, A. I.: Pneumatosis of the Colon. J.A.M.A. **148:** 1416–1417, April 19, 1952.

11. MCCORT, J. J.: Infarction of the Descending Colon Due to Vascular Occlusion; Report of Three Cases. New England J. Med. **262:** 168–172, Jan. 28, 1960.

12. NELSON, T. G., AND BOWERS, W. F.: Volvulus of the Cecum and Sigmoid Colon; Analysis of 9 Cases. Arch. Surg. **72:** 469–478, March 1956.

13. POOL, R. M., AND DUNAVANT, W. D.: Volvulus of the Sigmoid Colon. Ann. Surg. **133:** 719–725, May 1951.

14. RIGLER, L. G., AND LIPSCHULTZ, O.: Roentgenologic Findings in Acute Obstruction of the Colon, with Particular Reference to Acute Volvulus of the Sigmoid. Radiology **35:** 534–543, November 1940.

15. RITVO, M., AND GOLDEN, J. L.: The Roentgen Diagnosis of Volvulus of the Sigmoid with Intestinal Obstruction. Am. J. Roentgenol. **56:** 480–488, October 1946.

16. WOLF, B. S., AND MARSHAK, R. H.: Segmental Infarction of the Small Bowel. Radiology **66:** 701–706, May 1956.

SUMMARIO IN INTERLINGUA

Apparentia Inusual del Colon post Volvulo del Sigmoide

Es reportate un caso de volvulo del sigmoide tractate per intubation via un sigmoidoscopio. Un studio con clyster de barium tres dies post le detorsion demonstrava un large e redundante ansa del colon sigmoide con multiple serrationes al margines que habeva le apparentia de numerose micre ulceres. Le pellicula post-evacuatori monstrava un spissification del mucosa sigmoide, sed le sigmoidoscopia que esseva effectuate duo dies plus tarde produceva nulle evidentia de ulceration e permitteva le observation de solmente un leve injection mucosal.

Es opinate que iste alterationes esseva causate per edema mucosal resultante ab un embarasso del provision de sanguine al sigmoide durante le presentia del volvulo. Le lesion non esseva extense. Regeneration occurreva sin fibrosis.

Persistent Trigeminal Artery

A Method for Its Demonstration[1]

WILLIAM E. GANNON, M.D., and HARRY A. KAPLAN, M.D.

QUAIN (1) FIRST described a carotid-basilar anastomosis in 1844. Because of its close relationship to the gasserian ganglion and the fifth cranial nerve, this anastomosis has been called a persistent trigeminal artery (2). In the 3-mm. human embryo the entire brain receives arterial blood from the internal carotid artery system; the forebrain by the cephalad branches and the hindbrain mainly by the trigeminal artery. With the formation of the vertebral-basilar system to supply the hindbrain, the trigeminal artery is no longer necessary and usually regresses. This process is complete by the time the embryo reaches the 14-mm. stage (thirty-fifth day). Persistence of the artery in the adult may have clinical significance.

The primary purpose of this paper is to describe a method which may aid in the visualization of the persistent trigeminal artery during angiography.

Fig. 1. Case 1. Tilted lateral angiogram. The trigeminal artery can be seen arising from the internal carotid artery and joining the basilar artery. A normal posterior communicating artery is present.

CASE I: M. M., a 34-year-old white woman, was brought to the hospital because of acute alcoholism. No other history was obtained. Physical examination revealed numerous bruises about the head. The right pupil was larger than the left and reacted sluggishly to light; the corneal reflexes were diminished bilaterally. There were horizontal nystagmus, with the fast component to the left, and a left central facial paresis. Deep reflexes were increased in all extremities, and a left hemiparesis with bilateral Hoffman and Babinski signs was noted. The patient's temperature was 104°. The white blood count was 21,500 per cubic centimeter.

On the day following admission, a right carotid angiogram was obtained. Before the lateral view was made, the x-ray tube was inadvertently displaced and tilted toward the vertex of the skull. The top of the cranium was not visualized on the films. A persistent trigeminal artery, in addition to a normal-sized posterior communicating artery, was demonstrated (Fig. 1). With x-ray tube then positioned for a direct lateral exposure, the examination was repeated. This time the anomalous vessel was hidden by the density of the bone at the base of the skull (Fig. 2). The remainder of the study was negative.

CASE II: L. B., a 48-year-old Negro woman, was admitted to the hospital in a stuporous condition, because of a sudden onset of unconsciousness. For many years she had been known to be hypertensive. Examination revealed a soft-tissue swelling over the right forehead, slight nuchal rigidity, early bilateral papilledema, a left homonymous hemianopsia, depression of the left corneal reflex, a left flaccid hemiplegia, and a left Babinski sign.

A right carotid angiogram was at first considered to be essentially normal. It was noted, however, that the basilar artery, the posterior cerebral arteries, and the superior cerebellar arteries were opacified despite the presence of a normal posterior communicating artery (Fig. 3). The presence of a persistent trigeminal artery was suspected, and the examination was repeated with the x-ray tube angled toward the vertex of the skull. This time the persistent trigeminal artery could be clearly

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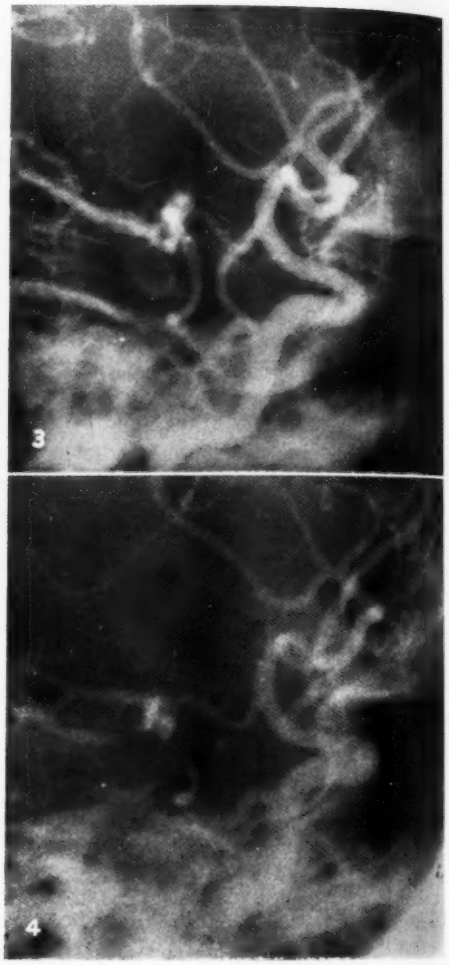
Fig. 2. Case I. Direct lateral angiogram. The basilar artery is again opacified but the trigeminal artery is hidden by the bony density at the base of the skull.

seen, superimposed on the bony density of the middle fossa of the skull (Fig. 4).

DISCUSSION

It was not until 1950, twenty-three years after the development of cerebral angiography by Egas Moniz and Almeida Lima, that the demonstration of a persistent trigeminal artery during angiography was reported by Sutton (3). Since then, cases of visualization of this vessel during angiography have been reported by Ecker, Sugar, Harrison and Luttrell (3 cases), Stenvers and Bannenberg, Kloss, Frugoni, Murtagh *et al.*, Schaerer, Poblete and Asenjo (2 cases), Zaclis, Wise, Mount and Taveras, Tartarini and Noceti, Saltzman (8 cases), Wiedenmann and Hipp (6 cases), and Jackson and Garza-Mercado (4–19).

The frequency of persistence of the trigeminal artery has been variously reported as 3 in 210 brain specimens (20), 1 in nearly 1,000 angiograms (3), 3 in 582 angiograms (6), 1 in nearly 600 angiograms (11), 1 in 750 angiograms (7), 2 in



Figs. 3 and 4. Case II. Fig. 3. Direct lateral angiogram. The anterior portion of the trigeminal artery could easily be confused with the external carotid branch overlying it. The posterior portion is hidden by the bony density at the base of the skull.

Fig. 4. Tilted lateral angiogram. The origin of the trigeminal artery from the internal carotid artery can be clearly seen. Its entire course and union with the basilar artery were visualized on the original roentgenogram.

828 angiograms (12), 6 in 7,382 angiograms (18), and 1 in 800 angiograms (19). In our own series we have found 3 additional cases in approximately 1,200 angiograms.

Many reasons have been advanced to explain why the trigeminal artery is not seen as often during angiography as at the autopsy table. We believe that it is mainly because the vessel is often obscured

by the bony density at the base of the skull. When the basilar artery is opacified down to the skull base during carotid angiography, the observer should be highly suspicious of a persistent trigeminal artery. If its presence or absence is significant in a particular case, the examination should be repeated with the x-ray beam angled toward the vertex or toward the feet. When the side under examination is next to the film, the beam should be angled 30° toward the vertex. By this maneuver the trigeminal artery is projected over the relatively uniform bony density of the floor of the middle fossa. The exposure factors remain the same as for a lateral cerebral angiogram.

SUMMARY

A method of demonstrating a persistent trigeminal artery during angiography is described. It consists of angling the x-ray tube toward the vertex of the skull or toward the feet, depending upon the relationship of the film to the side of the head under examination. The angulation permits the projection of the trigeminal artery over the fairly uniform density of the middle fossa of the skull.

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REFERENCES

1. QUAIN, R.: The Anatomy of the Arteries of the Human Body and Its Applications to Pathology and Operative Surgery, with Series of Lithographic Drawings. London, England, Taylor & Walton, 1844, p. 507.
2. PADGET, D. H.: Development of Cranial Arteries in the Human Embryo. Contrib. Embryol. (nos. 207–212) **32**: 205–262, 1948.
3. SUTTON, D.: Anomalous Carotid-Basilar Anastomosis. Brit. J. Radiol. **23**: 617–619, October 1950.
4. ECKER, A.: The Normal Cerebral Angiogram. Springfield, Ill., Charles C Thomas, 1951.
5. SUGAR, O.: Cited by Harrison and Luttrell (6).
6. HARRISON, C. R., AND LUTTRELL, C.: Persistent Carotid-Basilar Anastomosis. Three Arteriographically Demonstrated Cases with One Anatomical Specimen. J. Neurosurg. **10**: 205–215, May 1953.
7. STENVERS, H. W., AND BANNENBERG, P. M.: Een geval van blijvende anastomose tussen arteria carotis interna en arteria basilaris. Nederl. tijdschr. v. geneesk. **98**: 847–851, March 27, 1954.
8. KLOSS, K.: Persistierende Carotis-Basilaris-Anastomose als Ursache einer Subarachnoidalblutung. Zentralbl. f. Neurochir. **13**: 166–171, 1953.
9. FRUGONI, P.: Fifth International Neurological Congress. Lisbon, 1953, vol. 2, p. 21.
10. MURTAGH, F., STAUFFER, H. M., AND HARLEY, R. D.: A Case of Persistent Carotid-Basilar Anastomosis Associated with Aneurysm of the Homolateral Middle Cerebral Artery Manifested by Oculomotor Palsy. J. Neurosurg. **12**: 46–49, January 1955.
11. SCHAERER, J. P.: A Case of Carotid-Basilar Anastomosis with Multiple Associated Cerebrovascular Anomalies. J. Neurosurg. **12**:62–65, January 1955.
12. POBLETE, R., AND ASENJO, A.: Anastomosis carotido-basilar por persistencia de la arteria trigeminal primitiva. Neurocirugia **11** (no. 5): 1–5, 1955.
13. ZACLIS, J.: Persistência de anastomose carótido-basilar. A propósito de um caso revelado pela angiografia cerebral. Arq. neuro-psiquiat. **13**: 351–356, December 1955.
14. WISE, B. L.: Angiographic Demonstration of the Primitive Trigeminal Artery (Carotid-Basilar Anastomosis). Radiology **68**: 731–732, May 1957.
15. MOUNT, L. A., AND TAVERAS, J. M.: Arteriographic Demonstration of the Collateral Circulation of the Cerebral Hemispheres. Arch. Neurol. & Psychiat. **78**: 235–253, September 1957.
16. TARTARINI, E., AND NOCETI, D.: La persistenza dell'arteria trigeminale primitiva. Presentazione di un caso diagnosticato arteriograficamente. Sistema nerv. **9**: 137–144, May-June 1957.
17. SALTZMAN, G. F.: Patent Primitive Trigeminal Artery Studied by Cerebral Angiography. Acta radiol. **51**: 329–336, May 1959.
18. WIEDENMANN, O., AND HIPP, E.: Abnorme Kommunikationen zwischen dem Versorgungsgebiet der Arteria carotis interna und der Arteria basilaris (karotidobasiläre Anastomosen). Fortschr. a. d. Geb. d. Röntgenstrahlen **91**: 350–365, September 1959.
19. JACKSON, I. J., AND GARZA-MERCADO, R.: Persistent Carotid-Basilar Artery Anastomosis: Occasionally a Possible Cause of Tic Douloureux. Angiology **11**: 103–107, April 1960.
20. SUNDERLAND, S.: Neurovascular Relations and Anomalies at the Base of the Brain. J. Neurol., Neurosurg. & Psychiat. **11**: 243–257, November 1948.

SUMMARIO IN INTERLINGUA

Persistentia del Arteria Trigeminal: Un Methodo pro le Demonstration de Iste Vaso

Es describite un methodo pro demonstrar un persistente arteria trigeminal in le curso de angiographia. Le methodo es illustrate per le reporto de 2 casos. Illo consiste in un angulation del tubo de radios X verso le vertice del cranio o verso le pedes, in dependentia ab le relation inter le pellicula e le latere del capite sub examination. Le angulation permitte le projection del arteria trigeminal super le satis uniforme densitate del fossa central del cranio.

Interstitial Irradiation of Brain Tumors with Iridium 192[1]

NORMAN E. CHASE, M.D., HAROLD L. ATKINS, M.D., and JAMES W. CORRELL, M.D.

Interstitial irradiation of brain tumors has been attempted in the past with encouraging clinical results (1) but was abandoned because of technical difficulties. Satisfactory distribution of radon seeds is extremely difficult to achieve in the brain. Radium needles have a tendency to migrate in brain tissue because of their weight and require reoperation for removal.

Henschke in 1956 (2) described the use of iridium-192 seeds in nylon ribbons for interstitial radiation therapy. This technic has been modified for interstitial irradiation of intracerebral lesions.

Special requirements for interstitial sources in the brain are: (*a*) a simple method for suitable distribution; (*b*) satisfactory physical factors for proper dose rate; (*c*) sources and containers light in weight and flexible enough to prevent migration after implantation; (*d*) possibility of removal without operation.

The first two criteria are met by the Henschke ribbons. Modification was necessary to satisfy the other requirements. The greatest active length usually needed is under 8 cm., since the widest dimension of the cerebral hemisphere falls in this range.

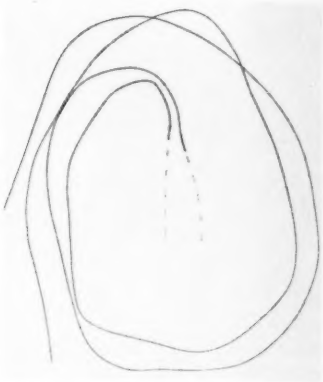

Fig. 1. This illustrates two of the nylon ribbons containing the active seeds with attached surgical silk. This modification of the Henschke ribbons may be obtained from the manufacturer by referring to "Iriditope for brain implantation."

Eight iridum seeds encased in steel, each equivalent in activity to approximately 0.5 mg. radium, are placed at 1-cm. intervals along the active segment

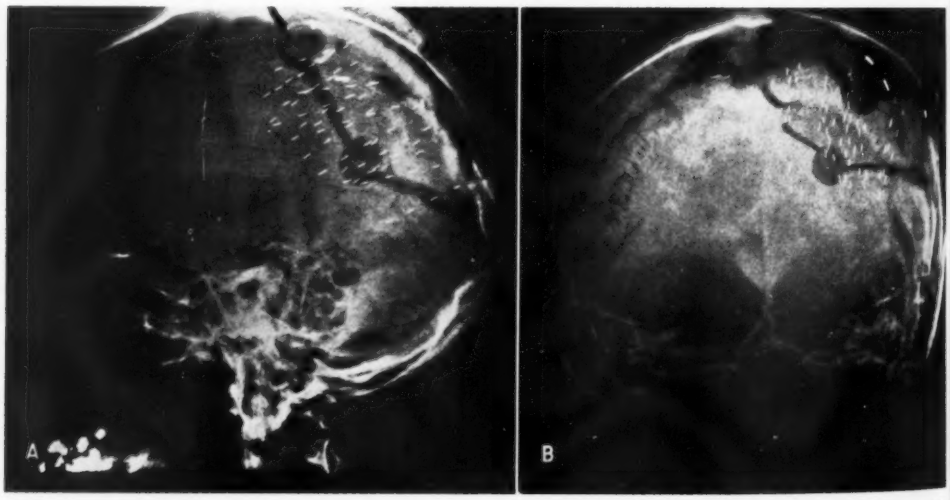

Fig. 2. Post-implantation roentgenograms showing the placement of iridium 192 in a 45-year-old man with recurrent glioblastoma multiforme in the right (non-dominant) parietal region. The implantation was carried out ten days after partial surgical resection of recurrent tumor, two hundred and forty-four days after the first wide surgical resection, which had been followed by x-ray therapy (4,000 r in twenty-eight days) and had resulted in several months of complete remission. Following interstitial irradiation (calculated dose of 6,000 r), improvement was evidenced by a partial return of neurological function; but eventual recurrence and death occurred two hundred and fifty-one days after the implantation. Postmortem examination showed that the tumor had widely invaded the brain stem and other mid-line structures beyond the limits of the implantation.

of the nylon ribbon. At the inactive end 00 black silk surgical thread is substituted for the nylon leader (Fig. 1).[2] The ribbons are implanted at craniotomy after surgical decompression of the tumor. An attempt is made to approximate a Paterson-Parker distribution of sources. The bone flap is replaced after a gap is rongeured at one edge. The loose silk leader is buried under the scalp.

Dose rate is calculated from measurements of source distribution on postoperative radiographs (Fig. 2), and a tumor dose of 5,000 to 7,000 r in four to seven days is administered. Removal of the implant is readily accomplished by reopening a portion of the skin incision and gently withdrawing the individual threads. Removal may be accomplished at the bedside and takes less than fifteen minutes.

One disadvantage of this manner of brain tumor irradiation is the relatively high radiation dose to nursing personnel concerned in the rather intense care which postoperative neurosurgical patients require. This can be offset by rotation of nurses and utilization of the patient's family in rendering the required services.

Several patients have received this form of therapy and initial appraisal is encouraging. It is now possible to deliver a greater therapeutic dose to brain tumors with minimal damage to normal structures.

REFERENCES

1. SACHS, E.: The Treatment of Glioblastomas with Radium. J. Neurosurg. **11:** 119–121, March 1954.

2. HENSCHKE, U. K.: Artificial Radioisotopes in Nylon Ribbons for Implantation in Neoplasms. Proc. Internat. Conf. Peaceful Uses of Atomic Energy **10:** 48, 1956.

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[1] From the Departments of Radiology and Neurosurgery, the Neurological Institute, Columbia-Presbyterian Medical Center, New York.

[2] Available from E. R. Squibb & Sons, as Iriditope for brain implantation.

EDITORIAL

Trends in Diagnostic Radiology

Today the possibilities for rehabilitation from or cure of many medical and surgical diseases are so promising that more and more refinement in diagnosis is required. Radiology perhaps more than any other branch of medicine has felt this pressure for definitive diagnosis. Many significant contributions in the development of specialized x-ray diagnostic technics have been made within the past few years. Many today are in the early clinical experimental stage. Others are still to reach the clinical level.

A tremendous amount of creative investigative activity has focused in recent years on the development of x-ray procedures that permit visualization of the arterial and venous systems of man, and today there remains no important vascular system that has not received intense radiologic scrutiny. Much of this creative investigation has resulted in fruitful clinical advantage, thus providing opportunities for the application of indicated medical or surgical remedial measures. To mention a few outstanding examples of x-ray diagnostic technics that have made important contributions to the better management or cure of some of the more common major congenital and acquired diseases, one may pay tribute to the development of venous angiocardiography, selective angiocardiography, intravenous aortography, coronary arteriography, percutaneous splenoportography, percutaneous transfemoral arteriography (the fundamental technic permitting selective visualization of many arterial systems), intraosseous venography, and nephrotomography.

These achievements have been the culmination of a tremendous activity, within the past decade, comprising a huge variety of radiologic studies involving the entire spectrum of cardiovascular disease. The cardiovascular system, though perhaps the principal recipient of this stimulating period of investigative enthusiasm, has by no means been the sole beneficiary. Bold and imaginative investigations have resulted in new knowledge and better understanding of many formerly perplexing problems involving the gastrointestinal tract and urinary, skeletal, and lymphatic systems.

The development of precision diagnostic x-ray examinations, frequently requiring knowledge and skill in the use of arterial catheters, diagnostic puncture needles, and catheters for insertion into spleen, liver, and kidneys, as well as forms of instrumental manipulation, has necessitated an ever increasing degree of specialization in diagnostic radiology. There has been a consequent trend toward the establishment of multiple subspecialties. This has been the inevitable result of the rapid growth of our specialty and the acquisition of huge stacks of information which requires special and careful study so that it can be distilled into useful knowledge. A reassuring precedence for this transformation in radiology is to be found in the development of well defined subspecialties in the older clinical disciplines of internal medicine and surgery, a process which in both is still continuing.

Progress in diagnostic radiology has contributed importantly to the present high quality of patient care practiced in our medical centers as well as many of our community hospitals. It has in addition, however, presented a challenge to our training programs. If we do not meet this challenge successfully, the present status of radiology as a major clinical discipline may well be in jeopardy. There is a need

now to reappraise our resident training programs and to consider the searching question: Are we providing the quality of training that the future of the specialty requires?

The requirements of the future in diagnostic radiology demand that the major training centers be capable of providing skilled instruction and experience in depth in such specialty areas as pediatric radiology, cardiovascular radiology, neuroradiology, and orthopedic radiology. In order to provide this type of training, the departments of radiology must themselves be adequately staffed and must be so organized that the most effective teaching in all specialty areas is possible. Of fundamental importance to the success of such a program is the necessity that the radiologists who are given the responsibility for training in areas requiring the use of instrumentation and manipulative skill be themselves expertly trained in those procedures. It is furthermore essential that the radiologist accept the responsibility for examination and that he control its conduct.

To provide such a corps of capable, experienced teachers is the present challenge to the radiology departments of the major teaching centers. If diagnostic radiology is to survive as a major clinical discipline, this challenge must be met quickly. The responsibility for providing an improved quality of resident training has placed a heavy strain on the teaching resources of many approved teaching programs. It seems doubtful, however, that the requirements of the future can be entirely met by our present traditional three-year residency, which is oriented for the radiologic generalist. This is a good program for the purpose for which it is intended, namely, to train physicians for the general practice of radiology. Furthermore, there is little doubt that because of geographical, social, and economic reasons this country will continue to need radiologic generalists for many more years. Nevertheless, there has been a general restlessness in teaching circles in recent years in respect to the traditional three-year program, a feeling that it is not adequate to meet the needs of the present. A number of University Departments have modified their three-year programs in an attempt to meet this challenge.

There is no question that the medical requirements of the immediate future will necessitate the creation of new resident training programs in both diagnostic radiology and therapeutic radiology. It would therefore seem that, in anticipation of the time when such new programs finally become realized, it would be well for those who will bear the brunt of these new training responsibilities to take inventory of their professional capability and to give thoughtful deliberation to the educational resources available to them. Complacency with the status quo does not satisfy the present and what has satisfied the past will not be enough for the future. Which way shall we go? Along the road that leads to greater clinical responsibility and independence or one that requires dependence and subordination?

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FORTY-SEVENTH ANNUAL MEETING: COMMERCIAL EXHIBITS

As a guide to the Commercial Exhibits, which form so important a feature of the Annual Meeting of the Radiological Society, the following brief accounts of the displays, prepared by the exhibitors themselves, are presented in advance.

Abbott Laboratories, North Chicago, Ill. (Booth 12): Abbott Laboratories will present their full line of radio-pharmaceuticals for complete application. Newer and experimental products will be featured for studies of metabolism in man. Use of radio-pharmaceuticals in red-cell uptake and *in vitro* measurement of thyroid function will be featured.

Albert Acan X-Ray, Inc., Detroit, Mich. (Booth 37): The Albert Acan X-Ray Solutions Services exhibit will feature maintenance and tank service of all manual and automatic units including X-Omat, Pakorol-X, Fisher and Rapidex processors. The radiologist has a choice of Ansco, du Pont, Med, or Kodak chemicals, standard or automatic type. A most efficient method of silver reclamation for automatic processors only will be displayed.

Ansco Division of General Aniline and Film Corporation, Binghamton, N. Y. (Booths 16 and 17): Ansco will display, in addition to its regular line of high-speed and non-screen x-ray films, the recently announced Ansco Dura-D and Dura-Speed intensifying screens. The availability of rounded corners on Ansco x-ray films for use in automatic processing equipment will also be highlighted. Accessory items for the radiologist will include the Ansco-File, a new system for handling radiographs during routing within the x-ray department, and the Ansco-Tainer film-carrying case for transporting exposed and unexposed films.

Atomic Energy of Canada Ltd., Ottawa, Ont. (Booths 26–27): The Commercial Products Division of Atomic Energy of Canada Ltd. will show a production unit as well as scale models of various cobalt teletherapy equipment of current design. A display of sample single- and double-welded capsules for high-specific-activity pellet cobalt-60 sources will also be featured. Catalogues and product literature will be available.

Automatic Seriograph Corporation, College Park, Md. (Booth 87): The Automatic Seriograph Corporation, a subsidiary of Litton Industries, Inc., will exhibit its new Model 110A of the Sanchez-Perez Universal Automatic Seriograph unit. This new unit has been redesigned for greater convenience, better quality, and improved appearance.

Bar-Ray Products, Inc., Brooklyn, N. Y. (Booths 105 and 106).

Barnes-Hind Barium Products Company, Sunnyvale, Calif. (Booth 38): The Barnes-Hind Barium Products Company will have a display of their highly micronized barium sulfate product, Barotrast, and the Barnes-Hind Pneumocolon for the administration of barium sulfate. Barotrast is an ideal all-purpose barium sulfate preparation which has established its position in the field of radiology by producing consistently better results than standard barium sulfate preparations.

Bell-Craig, Inc., New York, N. Y. (Booth 13): The Bell-Craig exhibit features a series of barium formulations (Ultrapaque, Baroloid, Raybar F, Raybar), oral cholagogues for duct demonstration in cholecystangiography (Neo-Cholex and Cholex), an aqueous contrast solution for cholangiography and hysterosalpingography (Medopaque), and plastic, disposable enema tips (Cly-Tip).

Buck X-Ograph Company, St. Louis, Mo. (Booths 91 and 92).

Carr Corporation, Santa Monica, Calif. (Booths 24 and 25): A front plumbing tank with new overhead dryer mounted on top will be exhibited by the Carr Corporation. The new overhead dryer is unique, eliminating the use of valuable floor space and utilizing wall and ceiling areas which would otherwise be useless. This dryer is run by a special drive motor which lowers the hanger rack over the wash section, making it possible for the technician to load film easily.

Coca-Cola Company, Atlanta, Ga. (Booth 7): Ice-cold Coca-Cola will be served throughout the course of the meeting through the courtesy and co-operation of the Coca-Cola Bottling Company of Chicago, Inc., and The Coca-Cola Company.

Continental X-Ray Corporation, Chicago, Ill. (Booths 114 and 115): Continental X-Ray Corporation will display Model SP-325 spot-film diagnostic unit with Multiplane 90-90 tilt table, Ultracon 300 ma at 125-kvp power unit with high-voltage selenium rectifiers, and Courier floor-to-ceiling tube stand.

Coreco Research Corporation, New York, N. Y. (Booth 101).

Lester A. Dine Company, Woodside, N. Y. (Booth 78): The sensational Eastman Kodak Startech close-up camera will be featured by the Lester A. Dine Company. This inexpensive camera is ideal for taking close-ups and, in addition, can be used for the copying of a whole or portion of an x-ray film. Amazing results are attained with a simplified set-up.

Dunlee Corporation, Bellwood, Ill. (Booths 88 and 89): The Dunlee Corporation will have on display rotating anode tubes in all kilovolt classifications, together with stationary anode inserts and valve tubes. Featured will be a complete line of beryllium window tubes.

E. I. du Pont de Nemours & Company, Inc., Wilmington, Del. (Booths 57–60): The E. I. du Pont de Nemours photo products exhibit will feature, with illustrative material, du Pont's contributions to radiology in over thirty years of service to the profession. Current contributions will be illustrated in the form of the "First a Physician" movie, du Pont *X-ray News*, du Pont educational grants, and training aids for x-ray schools. Pre-cornered medical x-ray film available in the thrift pack will also be displayed.

Eastman Kodak Company, Rochester, N. Y. (Booths 97, 98, 109, 110): The Kodak exhibit will show the latest types of medical x-ray products, such as films and chemicals. Both the M3 and the new M4 Kodak X-Omat Processors will be on display. There will also be a showing of technical aids and services.

Eureka X-ray Tube Corporation, Chicago, Ill. (Booth 83).

Field Emission Corporation, McMinnville, Ore. (Booth 113).

Oscar Fisher Company, Inc., Newburgh, N. Y. (Booths 65 and 66): The Oscar Fisher Company will exhibit the latest developments in its line of fully automatic x-ray processing equipment. These will include the smallest available sheet-film processor, a cinefluorographic film processor which was approved at the symposium for the processing of this material, as well as its older line of anhydrous dryers.

C. B. Fleet Company, Inc., Lynchburg, Va. (Booth 116): *A Simplified, Safe and Satisfactory Method of Preparation for Barium Enema Studies* is the title of a clinical report of a recently concluded series of 250 cases. Please visit Booth No. 116 for an abstract and for personalized instructions for patient distribution.

Forsyth X-ray Corporation, Chicago (Booth 90).

E. Fougera and Company, Hicksville, N. Y. (Booth 80): You are cordially invited to visit the Fougera exhibit, where product and clinical information and physician aids in radiology will be available. Informed attendants will be on hand to discuss your interests in various areas of diagnostic radiology and the application of Fougera x-ray contrast media to various procedures.

Franklin X-ray Corporation, Philadelphia, Penna. (Booth 100).

General Electric Company, X-Ray Department, Milwaukee, Wisc. (Booths 30–36): General Electric's X-Ray Department will display the latest advances in diagnostic x-ray equipment systems, including Teletrol, a unique remote-control x-ray unit; also the Fluoricon, an image-intensification system with cinefluorographic and TV facilities. Generating units and new supply and accessory items will also be exhibited.

Gordon Consultants, New York, N. Y. (Booth 45): Gordon Consultants are exhibiting the following items: vastly improved 1961 models of projectors for full-size x-ray films alone or with attachments for all other types of projection (except microscopic) including 35-mm. and 3 × 4-inch slides, opaque specimens, and full-size film scanning with a magnification of ×25; new "vest pocket" stereoscope for full-size films, now standard equipment for the U. S. Government.

Grune & Stratton, Inc., New York, N. Y. (Booth 39): Mr. Kurzer of Grune & Stratton will be on hand to show new books. Included will be: *An Atlas of Positive Contrast Myelography* by Bull; *Neuroradiology Workshop* by Jacobson, Davidoff, and Zimmerman in three volumes; *Artefacts and Handling and Processing Faults on X-ray Films* by Zimmer; *Diagnostic Roentgenology of the Digestive Tract Without Contrast Media* by Wolf, Khilnani, and Lautkin; and *Intra-Osseous Venography* by Schobinger. Among other important volumes there will also be displayed such classics as: Schinz *et al.*, *Roentgen-Diagnostics* (four volumes); Schinz *et al.*, *Roentgen-Diagnostics Progress*: Volume I; Schmorl and Junghanns, *The Human Spine in Health and Disease*; Lassrich *et al.*, *Pediatric Roentgenology*; Köhler, *Borderlands of the Normal and Early Pathologic in Skeletal Roentgenology*.

Halsey X-ray Products, Inc., Brooklyn, N. Y. (Booths 102 and 103).

High Voltage Engineering Corporation, Burlington, Mass. (Office No. 403).

Paul B. Hoeber, Inc., New York, N. Y. (Booth 44): On display at the booth of Paul B. Hoeber, Inc., will be the new third edition of *Physical Foundations of Radiology* by Glasser *et al.* Also, of special interest are Paul and Juhl's *Essentials of Roentgen Interpretation*, Shapiro and Janzen's *The Normal Skull*, and McLaren's *Modern Trends in Diagnostic Radiology*.

Hospital Microfilming, Pearl River, N. Y. (Booth 67): New viewers and readers for x-ray microfilm will be shown by Hospital Microfilming, along with a revised model of the popular x-ray microfilm camera. In addition, this year for the first time Type-X microfilm loaded in 35-mm. cartridges will be offered. Every radiologist should consider this new item for his personal collection of teaching films. Details and samples will be available at the booth.

Howdon Videx Products Corporation, Mount Vernon, N.Y. (Booth 64): Radiographic cones and collimators will be exhibited. Mr. Leonard F. Peyser will be present to answer questions pertaining to the progress and problems of close, beam-limiting technics. Films and data will be available. The problem of a light localizing collimator for operating-room x-ray equipment will be discussed.

Philip A. Hunt Company, Palisades Park, N. J. (Booth 61): The theme of the Philip A. Hunt Company exhibit will be "A Matter of Great Importance to Owners of X-O-Mat and Pako Roller Processors." Hunt Graph-O-Mat chemistry for automatic roller processors with particular emphasis on the most recent advance in rapid processing chemistry, Type 4 Graph-O-Mat Fixer, will be featured. This fixer is designed to promote complete and rapid drying of all films in all types of roller processors. Also featured will be the Hunt line of products for conventional processing.

Ilford, Inc., New York, N. Y. (Booth 76): The Ilford exhibit for 1961 will present Red Seal and Ilfex films used in typical diagnostic studies. Films for which Ilford Fast Tungstate Screens have been employed will also be shown. A variety of literature will be available and the Ilford technical representatives will be happy to discuss the application of Ilford products.

Lea & Febiger, Philadelphia, Penna. (Booth 15): At the Lea & Febiger booth be sure to see the following books: Epstein, *The Spine;* Fried, *Tumors of the Lungs and Mediastinum;* Jaffe, *Tumors and Tumorous Conditions of the Bones and Joints;* Carlson, *Veterinary Radiology;* Zimmerman, Netsky, and Davidoff, *Atlas of Tumors of the Nervous System;* Epstein, *Clinical Radiology of Abdominal Disorders;* Quimby, Feitelberg, and Silver, *Radioactive Isotopes in Clinical Practice;* Ritvo, *Chest X-Ray Diagnosis;* Ritvo, *Bone and Joint X-Ray Diagnosis;* Ritvo and Shauffer, *Gastrointestinal X-Ray Diagnosis;* Epstein and Davidoff, *Atlas of Skull Roentgenograms;* Davidoff and Epstein, *The Abnormal Pneumoencephalogram;* Robbins, *Roentgen Interpretation* (ready in 1962).

Leishman X-Ray Engineering Company, Los Angeles, Calif. (Booths 28, 73): The Leishman X-Ray Engineering Company exhibit will include: (1) Leishman Criterion spot filmer for General Electric Monarch; (2) new Leishman Easy-Loader spot filmer with Philips 9-inch II Adapter for Westinghouse Capri; (3) new Leishman Easy-Loader to show vertical loading for Profexray Emperor; (4) new Leishman Manumatic manually operated spot filmer with new internal phototimer for Keleket Nova-Matic.

Liberty Protective Leathers, Inc., Gloversville, N. Y. (Booth 108): The display of Liberty Protective Leathers Inc. consists of leaded-leather protective devices, including x-ray protective gloves, aprons, vests, and gonad and scrotal shields. These are designed for better protection of both the radiologist and patient against harmful radiation exposure.

Liebel-Flarsheim Company, Cincinnati, Ohio (Booth 99): Liebel-Flarsheim's new short-exposure, all-transistor timer will be available for inspection—no tubes, no gears, no warm-up period; physical dimensions approximately 2 1/2 inches wide × 4 1/8 inches high × 2 3/8 inches deep. Latest grid development and improvements in Bucky frames and cassette trays will also be shown.

LogEtronics, Inc., Alexandria, Va. (Booth 117): An electronic x-ray copying instrument which produces photographic copies with improved visibility of x-ray detail, LogEtronic Contact Printer, and illustrative LogEgram results will be displayed.

Low X-Ray Corporation, New York, N. Y. (Booths 50–52): Low X-Ray Corporation is the exclusive United States distributor for Gevaert films. Their exhibit will contain Gevaert medical x-ray film in the most complete line of speeds, types, and packing. Included will be: high-speed screen film (Gevaert Curix); ultraspeed screen film (Gevaert Curix Rapid); packed interleaved (25s–75s and Econopac 300s); non-interleaved (100s and Econopac 500s); individually packed screen film (Gevaert Curix Unipac, 25s); individually packed nonscreen film (Gevaert Osray Unipac, 25s); and photoroentgen and cine-rolls and cut sheets; Gevaert Scopix.

Machlett Laboratories, Inc., Springdale, Conn. (Booths 111 and 112): The Machlett Laboratories, Inc., will exhibit its new image-intensifier tubes, Dynascope "6" and Dynascope "9," which combine high brightness levels with high resolution. Shown also will be several of the company's rotating anode tubes, including the Dynamax "50," a high-speed, grid-controlled tube.

Mallinckrodt Chemical Works, St. Louis, Mo. (Booth 94): Ditriokon, Mallinckrodt's new contrast medium for angiocardiography, will be featured at Booth 94. Ditriokon is being extremely

well received because of its low viscosity, high concentration, and minimal side reactions. Other contrast media being featured include Miokon for intravenous urography, Pyelokon-R for retrograde pyelography, and Thixokon for urethrography.

Mattern X-ray Division of Land-Air, Inc., Chicago, Ill. (Booths 74 and 75): Mattern X-ray Division of Land-Air, Inc., will display and demonstrate the Mattern Sovereign 500-150 kv control featuring 1/120 sec. electronic timing, operation of three x-ray tubes, and up to five Buckys. The generator is designed especially for angiocardiography. The Mattern Sovereign 90/90 x-ray table with a power-driven table top will also be featured.

Donald McElroy, Inc., Chicago, Ill. (Booth 29): Booth 29 will be attended by representatives of Donald McElroy, Inc., and will contain examples of, and information about, the applications for used x-ray film and assistance in the sale and handling of films to Donald McElroy, Inc.

Micro X-Ray Recorder, Inc., Chicago, Ill. (Booth 119): Micro X-Ray Recorder, Inc., will feature over 65 series of 2 × 2-inch medical teaching slides on various subjects, compiled from the files of leading specialists and institutions. A Micro X-Ray Recorder and accessories for the microfilming of films, records, charts, etc., and the PV-501 projector-viewer for cool projection of film strips and slides will also be shown.

Mid-West Glove Company, Inc., Chicago, Ill. (Booth 79).

Norelco-North American Philips Company, Inc., New York, N. Y. (Booths 53–56): The Norelco-North American Philips Company exhibit will include a range of new 125-kv and 150-kv x-ray controls and will feature medical television and pulsed cineradiographic systems with the newest Philips 9-inch image intensifier. Newly developed turret lens mounts for greater flexibility in 16- and 35-mm. cineradiography, together with the 70-mm. camera, will be shown. Qualified personnel with specialized experience in cineradiographic technics will be available to discuss your equipment requirements.

Nuclear-Chicago Corporation, Des Plaines, Ill. (Office No. 402).

Nuclear Consultants Corporation, St. Louis, Mo. (Booth 68): Nuclear Consultants Corporation will feature three of its major contributions to the field of nuclear medicine. They are: (1) the development of individual dose sources which enable the physician to purchase more realistically and reduce his inventory and radiation expense; (2) the establishment of local service to the major portion of the country; (3) the development of Cobium® used to supplement or replace radium.

Old Delft Optical Company, Inc., Hicksville, N. Y. (Booths 69 and 70): The Old Delft Optical Company will exhibit a high-speed 4 × 4-inch Odelca camera specifically designed for radiological functional diagnostics. This camera features automatic film feed of 4 × 4-inch cut films at rates up to six exposures per second. A total of 40 exposures can be made automatically during any one study.

Orthopedic Frame Company, Kalamazoo, Mich. (Booth 77): The Axio-Chair will be demonstrated at the booth of the Orthopedic Frame Company. Three new diagnostic technics recently introduced utilize axial rotation: axioencephalography, contrast ventriculography, and axial cervico-cranial myelography. The Garcia-Oller Axioencephalography Chair allows all position changes to be electrically controlled and performance of the entire examination in a sitting position.

Pako Corporation, Minneapolis, Minn. (Booths 41–43): Pako will display both manual and automatic roller-type processing equipment. The new Pakorol-XM will be shown for the first time. This small unit provides roller-type automatic processing in seven minutes. Associate controls and accessories for the x-ray department will be shown.

Physicians Technical Equipment Company, Milwaukee, Wisc. (Booth 104).

Picker X-Ray Corporation, White Plains, N. Y. (Booths 18–23; 95–96).

Profexray, Inc., Maywood, Ill. (Booths 81 and 82): A feature of the Profexray exhibit will be the new Profexray 15°–90° fully enclosed table with the new Profexray spot-film device. Also to be introduced is a distinctively new control which will be exhibited with the Emperor 90°–90° table.

Radiology, Detroit, Mich. (Booth 125): RADIOLOGY, the official publication of the Radiological Society of North America, has prepared an exhibit of historical interest, with charts showing the advances in diagnostic and therapeutic radiology over the past two decades or more. These graphic representations will be supplemented by some interesting early publications from the files of the Society's Historian.

Radium Chemical Company, Inc., New York, N. Y. (Booth 14): The Radium Chemical Company will present modern cervical-uterine radium applicators. The latest instruments and accessories for the handling and application of radium and radon will be demonstrated by company

representatives. New protective equipment, including that for transportation, storage, and handling of radium in hospitals and offices, will also be featured.

Schick X-Ray Company, Inc., Chicago, Ill. (Booth 107): Schick X-Ray Company will demonstrate a model of the new Mimer x-ray unit which is manufactured by Elema-Schönander. This equipment finds its special application in neuroradiology. There will also be some radiographs taken with the new Orthopantomograph (made in Helsinki, Finland) which permits single-exposure radiographs of the full mouth in as short a time as fourteen seconds.

Frank Scholz Corporation, Boston, Mass. (Booth 93).

Siemens New York, Inc., X-Ray Division, New York, N. Y. (Booths 84–86): Siemens New York Inc., will display a revolutionary, fully automatic three-phase generator, the Triomat, and a new 7-inch mobile image-intensifier unit with TV monitor set. In addition, the well introduced Tridoros 5 three-phase generator will be shown together with a standard radiographic-fluoroscopic table and a radiographic multipurpose Bucky table.

Standard X-Ray Company, Chicago, Ill. (Booths 8–11): The latest developments in x-ray tables and machines will be on exhibition at the booth of Standard X-Ray Company. The new Ultima-105 table will be demonstrated by attendants, who will point out its many desirable features. Please stop and discuss any of your x-ray problems with us.

Thuresson-Angrabright-Bennett, Inc., Skokie, Ill. (Booth 71): Thuresson Angrabright-Bennett will exhibit a remarkably compact and precise overhead tube crane unit known to some in the profession but worth examination by all. This design encompasses the many aspects of full flexibility and demonstration of accurate focal spot size on radiographs by virtue of unique stability. Another item exhibited by this company will be the Cephal-X Cranial Radiographic Instrument designed with the neuroradiologist in mind. With this unit skull radiography can be accomplished with vernier accuracy of all adjustments and angulations.

Tracerlab Keleket, Inc., Waltham, Mass. (Booths 120–124): All radiologists are invited to the demonstration of equipment at the Tracerlab booth. This will include the newly developed Nova-Matic line, an image intensifier, a high-kv generator, and a full line of high-performance equipment. Clinical diagnostic instruments, automatic printing devices, and unique twin-film service will also be featured.

United States Radium Corporation, Morristown, N. J. (Booth 72): The Radelin Division of The United States Radium Corporation will feature Radelin® Aluminized x-ray screens which provide dual protection against stains and static in addition to maximum detail, unmatched abrasion resistance, moisture-humidity protection, and longer useful service life.

Victoreen Instrument Company, Cleveland, Ohio (Booths 62 and 63): The Victoreen exhibit will include the Victoreen Condenser r-Meter, new low-energy survey meter for radiation measurement over broad range from 6.5 kev to 1.2 Mev, medical x-ray measurement instruments, probes and chambers, personnel dosimeters, and survey meters, as well as a complete line of detectors, shields and manual sample changers, and new Vicount scaler.

Westinghouse Electric Corporation, Baltimore, Md. (Booths 1–6): Westinghouse will exhibit two new designs: Televex, a closed-circuit image Orthicon television system with optimal 16-mm. or 35-mm. cinefluorography, and Chesapeake, a multipurpose x-ray unit adaptable for most radiographic procedures. Also on display will be the Capri radiographic fluoroscopic table, Nassau spot-film device, Sierra overhead tube support, and Riviera 500-ma, 150-kv control.

Winthrop Laboratories, New York, N. Y. (Booth 40): Winthrop Laboratories cordially invites you to visit their booth at which the following product will be featured: Hypaque 50 per cent, dependable, well tolerated contrast medium for excretion urography, vasography, operative cholangiography, hysterosalpingography, and retrograde urography. Also available are Hypaque-M, 90 per cent, and Hypaque-M, 75 per cent, for angiocardiography, nephrotomography, hysterosalpingography, and selected cases of peripheral angiography.

Wolf X-Ray Products, Inc., Brooklyn, N. Y. (Booths 46–49): Wolf X-Ray Products, Inc., will devote its spacious exhibit area to a comprehensive line of x-ray protective and processing accessories. Among the highlights will be the lead vinyl washable aprons, new "standard" cassette, a noncorrosive Fiberglas safelight, and a new line of insulated developing tanks.

Year Book Publishers, Inc., Chicago, Ill. (Booth 118): Year Book Medical Publishers' complete line of books, featuring those of special interest to radiologists, will be on display. Among the many books available for inspection will be Caffey's *Pediatric X-Ray Diagnosis,* new 4th edition; Fields and Seed's *Clinical Use of Radioisotopes,* new 2nd edition; Glasser's *Medical Physics;* the new *Year Book of Radiology;* Lusted and Keats' *An Atlas of Roentgenographic Measurement.*

ANNOUNCEMENTS AND BOOK REVIEWS

AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology held a special convocation in São Paulo on Wednesday, Sept. 6, 1961, to confer honorary membership on Dr. Luis Arrieta-Sanchez, editor of Radiología, Panama; Dr. Nicola C. Caminha, President of the Brazil College of Radiology, Rio de Janeiro, Brazil; Dr. Antonio Pinto-Vieira, Director of the Institute of Cancer, Rio de Janeiro. The convocation was presided over by Philip J. Hodes, M.D. E. P. Pendergrass, M.D., acted as Chairman of the Board of Chancellors, and Ross Golden, M.D., as Sergeant of Arms. J. A. del Regato, M.D., read the citations in Portuguese.

CLEVELAND RADIOLOGICAL SOCIETY

The new officers of the Cleveland Radiological Society are: Charles J. Miller, Jr., M.D., Akron, President; Daniel R. Keating, M.D., Cleveland, Vice-President; Ward D. Heinrich, M.D., Huron Road Hospital, Cleveland 12, Ohio, Secretary-Treasurer. The Society meets the fourth Monday of October, November, January, February, March, and April.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI

The Radiological Society of Greater Cincinnati has recently installed the following officers: Eli Rubenstein, M.D., President; W. Donald Janney, M.D., Vice-President; and William C. Duffey, M.D., St. Elizabeth Hospital, Covington, Ky., Secretary-Treasurer.

EAST TENNESSEE RADIOLOGICAL SOCIETY

At a recent meeting of the East Tennessee Radiological Society the following officers were elected; President, James Jacob Range, M.D., Johnson City; President-Elect, Clifford L. Walton, Jr., M.D., Knoxville; Vice-President, Thomas S. Long, M.D., Lookout Mountain; Secretary-Treasurer, J. Marsh Frere, Jr., M.D., 8008 Bennington Drive, Knoxville.

SECTION ON RADIOLOGY ILLINOIS STATE MEDICAL SOCIETY

The present officers of the Section on Radiology of the Illinois State Medical Society are as follows: Homer Van Landingham, M.D., Rockford, Chairman; Howard C. Burkhead, M.D., 130 Dempster St., Evanston, Secretary.

MINNESOTA RADIOLOGICAL SOCIETY

The Minnesota Radiological Society officers for the current year are Rolf M. Iverson, M.D., of Minneapolis, President, and Frank J. Anderson, M.D., 810 E. 27th Street, Minneapolis, Secretary-Treasurer.

NEVADA RADIOLOGICAL SOCIETY

Recently elected officers of the Nevada Radiological Society are: President, Harry B. Gilbert, M.D., Reno; Secretary, George F. Fraser, M.D., 2020 W. Charleston, Las Vegas; Councilor to the American College of Radiology, Robert M. Taylor, M.D., Las Vegas.

Due to the geographical separation of the members, it has been determined that quarterly northern and southern sectional meetings will be carried on through the year. The next annual meeting, to be held in conjunction with that of the Nevada State Medical Association, will be in Las Vegas in the fall of 1962.

OHIO STATE RADIOLOGICAL SOCIETY

At the last meeting of the Ohio State Radiological Society, the following were elected to office: James G. Tye, M.D., Dayton, President; Paul D. Meyer, M.D., Columbus, President-Elect; Chapin Hawley, M.D., 927 Carew Tower, Cincinnati 2, Secretary; Delbert A. Russell, M.D., Elyria, Treasurer.

PITTSBURGH ROENTGEN SOCIETY

The following officers have been elected by the Pittsburgh Roentgen Society for the year 1961–62: President, T. B. Childs, M.D.; Vice-President, D. S. Greenberg, M.D.; Secretary, R. H. Smith, Jr., M.D., 265 46th Street, Pittsburgh 1; Treasurer, J. H. Griffin, M.D.; Councilor to the American College of Radiology, P. M. Feltwell, Jr., M.D.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

At the recent annual meeting of the Rocky Mountain Radiological Society, the following officers were elected: President, Thomas J. Kennedy, M.D., Denver, Colo.; President-Elect, Vernon L. Bolton, M.D., Colorado Springs, Colo.; 1st Vice-President, John A. Wilson, M.D., Tucson, Ariz.; 2nd Vice-President, Cyrus O. Hansen, M.D., Minneapolis, Minn.; Secretary-Treasurer, John H. Freed, M.D., 4200 East Ninth Ave., Denver 20, Colo.; Historian, H. Milton Berg, M.D., Bismarck, N. Dak. Mark S. Donovan, M.D., Denver, Colo., Grant P. Raitt, M.D., Billings, Mont., and Clarence N. Sorensen, M.D., Scottsbluff, Nebr., comprise the Executive Committee.

The next annual meeting of the Society will be held in Denver at the Denver Hilton Hotel on Aug. 16–18, 1962.

UPPER PENINSULA RADIOLOGICAL SOCIETY

The current President of the Upper Peninsula (Michigan) Radiological Society is T. Boyd Bolitho, M.D., Marquette. The Acting Secretary is Douglas W. Erickson, M.D., 101 South Fourth Street, Ishpeming.

WEST VIRGINIA RADIOLOGICAL SOCIETY

The West Virginia Radiological Society recently chose as officers for the coming year: Hubert A. Shaffer, M.D., Morgantown, President; Rex Dauphin, M.D., Parkersburg, Vice-President; Karl J. Myers, M.D., The Myers Clinic-Broaddus Hospital, Philippi, Secretary-Treasurer; Joseph L. Curry, M.D., Wheeling, Councilor to the American College of Radiology; J. Dennis Kugel, M.D., Charleston, Alternate Councilor. The following were elected members of the Executive Committee: J. D. H. Wilson, M.D., Clarksburg; Arthur E. Levy, M.D., Williamson.

WISCONSIN RADIOLOGICAL SOCIETY

At the annual meeting of the Wisconsin Radiological Society in September, the following officers were elected: President, John H. Juhl, M.D., Madison; President-Elect, Hobart H. Wright, M.D., Madison; Secretary-Treasurer, Howard G. Bayley, M.D., 116 Iroquois Parkway, Beaver Dam; Councilor to the American College of Radiology, Irving I. Cowan, M.D., Milwaukee; Alternate, Ralph C. Frank, M.D., Eau Claire. E. Dale Trout, Ph.D. (Physics), Milwaukee, and John R. Cameron, Ph.D. (Physics), Madison, were elected to Honorary Membership.

SECOND INTERNATIONAL CONGRESS OF RADIATION RESEARCH

Attention is again called (see Radiology **75:** 964, 1960) to the Second International Congress of Radiation Research to be held at Harrogate, Yorkshire, England, Aug. 5–11, 1962. Readers are reminded that the deadline for receipt of abstracts and for registration at the standard fee (£8 or $24.00) is Jan. 15, 1962. All inquiries and communications should be addressed to Dr. Alma Howard, Secretary-General, Mount Vernon Hospital, Northwood, Middlesex, England. Congress headquarters will be the Majestic Hotel, where many of the sessions will be held.

The Radiation Research Society, in co-operation with the National Academy of Sciences-National Research Council, is exploring possibilities for providing partial travel support to qualified participants. Applications must be submitted prior to Feb. 1, 1962. Forms for this purpose are available from the Committee on Travel Grants, Room 319, 2101 Constitution Ave., N. W., Washington 25, D. C.

Books Received

Books received are acknowledged under this heading and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

RADIOGRAPHIC ANATOMY OF THE HUMAN SKELETON: A HANDBOOK FOR RADIOGRAPHERS. By W. H. JOHNSON, F.S.R., Lecturer in Radiographic Anatomy, 1940–1956, for the Society of Radiographers Membership Examination at the Ilford Department of Radiography and Medical Photography, Tavistock House, London, and J. A. KENNEDY, M.B., M.R.C.S., D.M.R., D.M.R.D., Lecturer in Radiological Anatomy, King's College, University of London; Senior Radiologist, St. Helier Hospital, Carshalton, England. Foreword by K. C. Clark, M.B.E., Hon. F.S.R. A volume of 280 pages, with 233 figures. Published by The Williams & Wilkins Company, Baltimore 2, Md., 1961. Price $10.00.

THE FUNDAMENTALS OF X-RAY AND RADIUM PHYSICS. By JOSEPH SELMAN, M.D., Clinical Assistant Professor of Radiology, University of Texas, Southwestern Medical School; Director, School for X-ray Technicians, Tyler Junior College; Director, Radiology Department, Medical Center Hospital; Attending Staff in Radiology, Mother Frances Hospital; Consultant in Radiology, East Texas Tuberculosis Hospital, Tyler, Texas. A volume of 364 pages, with numerous figures and 9 tables. Published by Charles C Thomas, Springfield, Ill., 3d ed., 1961. Price $8.50.

FORMULATING X-RAY TECHNICS. By JOHN B. CAHOON, R.T., F.A.S.X.T., Assistant Professor of X-Ray Technology, Duke University Medical Center, Durham, N. C. A volume of 352 pages, with 100 figures. Published by Duke University Press, Durham, N. C., 5th ed., 1961. Price $7.50.

ROENTGENOGRAPHIC CEPHALOMETRICS. PROCEEDINGS OF THE SECOND RESEARCH WORKSHOP CONDUCTED BY THE SPECIAL COMMITTEE OF THE AMERICAN ASSOCIATION OF ORTHODONTISTS. Edited by J. A. SALZMANN, D.D.S., Chairman, Special Committee on Roentgenographic Cephalometrics of the American Association of Orthodontists. A volume of 196 pages with 53 figures. Published by J. B. Lippincott Company, Philadelphia, Penna., 1961. Price $4.75.

SELECTED TOPICS IN RADIATION DOSIMETRY. PROCEEDINGS OF THE SYMPOSIUM ON SELECTED TOPICS IN RADIATION DOSIMETRY, SPONSORED BY THE

INTERNATIONAL ATOMIC ENERGY AGENCY AND HELD IN VIENNA, 7–11 JUNE 1960. A volume of 686 pages, with numerous figures and tables. Published by International Atomic Energy Agency, Kaerntnerring, Vienna 1, Austria, 1961. Distributed in the United States by National Agency for International Publications, Inc., and UNESCO Publications Center, 801 Third Avenue, New York 22, N. Y. Price $9.50.

IONIZING RADIATION AND HEALTH. By BO LINDELL, Institute of Radiophysics, Stockholm, Sweden, and R. LOWRY DOBSON, Chief Medical Officer, Radiation and Isotopes, World Health Organization, Geneva, Switzerland. Public Health Papers No. 6. A monograph of 82 pages, with 27 tables. Published by World Health Organization, Geneva, Switzerland, 1961. Distributed in the United States by Columbia University Press, 2960 Broadway, New York 27, N. Y. Price $1.00.

ANNUAL REPORT ON THE RESULTS OF TREATMENT IN CARCINOMA OF THE UTERUS. TWELFTH VOLUME. STATEMENTS OF RESULTS OBTAINED IN 1945 TO 1954, INCLUSIVE (COLLATED IN 1960). Edited by DR. H.-L. KOTTMEIER. Published under the patronage of the International Federation of Gynecology and Obstetrics, General Secretary: Professor H. de Watteville, Geneva. Sponsored by the American Cancer Society; British Empire Cancer Campaign; Cancerföreningen, Stockholm; Damon Runyon Memorial Fund, New York; Deutscher Zentralausschuss für Krebsbekämpfung und Krebsforschung; Landsforeningen mot Kreft, Oslo; National Cancer Institute of Canada; Österreichische Krebsgesellschaft; Œuvre nationale belge de lutte contre le cancer. A volume of 336 pages, with numerous tables and diagrams. Stockholm 60, Sweden, 1961.

BRITISH COLUMBIA CANCER INSTITUTE, VANCOUVER: FIVE YEAR RESULTS OF TREATMENT, 1946–54, WITH A SYNOPSIS OF TREATMENT POLICY 1961. By A. MAXWELL EVANS, M.D., C.M., D.M.R.E., Director, British Columbia Cancer Institute, Clinical Assistant Professor, Department of Surgery, University of British Columbia. A volume of 270 pages, with numerous tables. Free of charge upon application to the Director of the British Columbia Cancer Institute, 2656 Heather Street, Vancouver 9, B. C.

THE CHEMICAL AND BIOLOGICAL ACTION OF RADIATIONS (ACTIONS CHIMIQUES ET BIOLOGIQUES DES RADIATIONS). Edited by N. HAÏSSINSKY. Vol. V. I. Mechanism of the Radiolysis of Water by Gamma Rays or Electrons. By A. O. Allen. II. Action des rayons alpha sur les solutions aqueuses. By J. Pucheault. III. Diffusion Kinetics in Radiation Chemistry. By A. Kuppermann. IV. Mass Spectrometry and Radiation Chemistry. By D. P. Stevenson and D. O. Schissler. A volume of 278 pages, with numerous figures and tables. Published by Academic Press, Inc., New York, N. Y., and London, England; Masson et Cie, Paris, 6e, 1961. Price $8.00; 64s.

LES CANCERS DU MASSIF MAXILLAIRE SUPÉRIEUR. ÉTUDE ANATOMO-CLINIQUE ET THÉRAPEUTIQUE. By P. C. HUET, Otorhinolaryngologiste des Hôpitaux de Paris et de l'Institut Gustave-Roussy, and S. STEFANI, Assistant étranger de l'Université de Paris; Résident de radiothérapie à l'Institut Gustave-Roussy. A paper-bound volume of 260 pages, with 57 figures and numerous tables. Published by Masson et Cie, Paris, 6e, 1961. Price 50 NF.

LES OSTÉO-ARTHROPATHIES NERVEUSES. By A. M. RECORDIER, P. MOUREN, and G. SERRATRICE. Preface by Prof. L. van Bogaert. A volume of 170 pages, with 50 figures. Published by Expansion scientifique française, 15, rue Saint-Benoit, Paris, 6e, 1961. Price 28 NF; postpaid 29.10 NF.

RŒNTGENTHÉRAPIE ET ÉLECTROTHÉRAPIE DES AFFECTIONS DE LA PEAU; INDICATIONS ET TECHNIQUES. By F. LEPENNETIER, Médecin électroradiologiste honoraire des Hôpitaux de Paris, ancien Chef du Service Central d'électro-radiologie de l'Hôpital Saint-Louis, and H. RABEAU, ancien Chef de Laboratoire à l'Hôpital Saint-Louis, Dermatologiste de l'Hôpital Américain de Paris. A volume of 524 pages, with 109 figures. Published by Masson et Cie, Paris, 6e, 1961. Price, paper-bound 62 NF; cloth-bound, 72 NF.

ILEUS: KLINIK, RADIOLOGIE UND THERAPIE. Edited by R. NISSEN, Basel, and E. HAFTER, Zürich. Vorträge gehalten an der 25. Jahresversammlung der Schweizerischen Gesellschaft für Gastroenterologie und an der ausserordentlichen Tagung der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, in Zürich 29. September–1. Oktober 1960. Bibliotheca Gastroenterologica, Fasc. 3. Supp. to Gastroenterologia. A paper-bound symposium of 112 pages with 43 figures. Published by S. Karger, Basel, Switzerland, 1961. American representative, Albert J. Phiebig, P. O. Box 352, White Plains, N. Y. Price S. Fr. 22.—($6.00).

WIEDERHERSTELLUNGSCHIRURGIE UND TRAUMATOLOGIE, JAHRBUCH. RECONSTRUCTION SURGERY AND TRAUMATOLOGY, ANNUAL SURVEY. CHIRURGIE RÉPARATRICE ET TRAUMATOLOGIE, ANNUAIRE. Volume 6. Edited by M. LANGE, München. A volume of 140 pages, with 56 figures and 7 tables. Published by S. Karger, Basel, Switzerland, 1961. American representative: Albert J. Phiebig, P. O. Box 352, White Plains, N. Y. Price $11.00.

SUBTRAKTION. By Prof. Dr. B. G. ZIEDSES DES PLANTES, Amsterdam. A monograph of 72 pages, with 160 illustrations on 59 figures. Published by Georg Thieme, Stuttgart, Germany, 1961. Distributed in the United States and Canada by Intercontinental Medical Book Corporation, New York 16, N. Y. Price DM 28.—($7.00).

BRONCOSCOPIA: PRINCIPÎ DI DIAGNOSTICA E ATLANTE DI FOTOGRAFIA ENDOSCOPICA. By LUCIANO CATTANEO, Clinica otorinolaringoiatrica del l'Università di Pavia, and LUCIO DI GUGLIELMO, Istituto di Radiologia dell'Università di Pavia. A volume of 400 pages, with 312 figures. Published by Il Pensiero scientifico, Rome, Italy, 1961. Price L. 15,000.

Book Reviews

A MANUAL FOR NUCLEAR MEDICINE. By E. R. KING, Captain, MC, U. S. Navy, and T. G. MITCHELL, Lieutenant, MSC, U. S. Navy. With a Foreword by B. W. Hogan, Rear Admiral, MC, U. S. Navy, Surgeon General of the Navy. A volume of 406 pages, with 80 figures. Published by Charles C Thomas, Springfield, Ill., 1961. Price $13.50.

The arrangement of this book is unusual. It begins with applications of radioisotopes to medical diagnostic problems, interspersed with some discussion of equipment, continues with a brief discussion of physical principles, then takes up protection, and concludes with a course of laboratory exercises. It would seem more logical to start with theory, follow this with experiments, and finally progress to clinical applications.

Apparently the book grew out of the training program at the National Naval Medical Center at Bethesda. The laboratory section refers to equipment in use there, in terms which sometimes make it difficult to transfer directions to other equipment.

The work might best be described as a manual of technics, without much discussion as to the reason for the choice of method under any particular circumstances. Bibliographies appended to some chapters enable the reader to become aware of other technics, but he is left with the problem of selection.

Radiologists and physicists will find this treatise too dogmatic and lacking in theory for their purposes.

LA GROSSE TUBÉROSITÉ DE L'ESTOMAC NORMALE ET PATHOLOGIQUE: ÉTUDE CLINIQUE ET RADIOLOGIQUE. By T. SCHOPS. Preface by Dr. René A. Gutmann. A volume of 574 pages, with 910 illustrations on 475 figures. Published by G. Doin & Cie, 8, place de l'Odéon, Paris, 6e, 1961. Price 125 NF.

That subdiaphragmatic portion of the stomach which fills with air with the patient upright (called, among other names, *fundus*, or *la grosse tubérosité*, as in the present work) very often is not accorded the attention it deserves in routine gastrointestinal studies. It takes second place to the more accessible, and more often disturbed, antrum and duodenum. But abnormalities in the fundus, harmless and otherwise, are not rare, and this book portrays them well. After studying it, the reader cannot fail to regard this segment of the digestive tract with renewed interest and respect.

After a preliminary discussion of the gross and radiologic anatomy, the author takes up peptic ulcer, diverticula, cancer, benign tumors, varices, gastritis, absence of the left lobe of the liver and its effect on the air pocket, hiatal hernia, eventration, and cascade stomach. The clinical and radiologic pictures, pathology, and treatment are reviewed. The illustrations, including the roentgen reproductions, are excellent, the printing is good, and the French is not difficult. This book, essentially an atlas, should be accessible to all those doing gastrointestinal studies. Its perusal is well worthwhile.

THE AMERICAN BOARD OF RADIOLOGY

The Spring 1962 examination of the American Board of Radiology will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, June 18–22, inclusive, 1962. The deadline for filing applications is Jan. 1, 1962. A special examination in Nuclear Medicine for Diplomates in Radiology or Therapeutic Radiology and an examination in Radiological Physics will be held if there are sufficient applications.

The Fall 1962 examination will be held at the Pioneer Hotel, Tucson, Ariz., the first week in December; the deadline for filing applications is July 1, 1962. Please note that at this session Nuclear Medicine will become a mandatory part of the examination. All candidates, excluding re-examinees, who are applying for examination in Radiology or Therapeutic Radiology for the December 1962 session or thereafter *must submit a Nuclear Medicine application* in addition to their basic application. This applies even to those applicants whose basic applications are on file but who will not yet have appeared for examination.

H. Dabney Kerr, M.D.
Secretary

ABSTRACTS OF CURRENT LITERATURE

ROENTGEN DIAGNOSIS

The Head and Neck

The Chest

The Heart and Blood Vessels

The Digestive System

The Musculoskeletal System

Gynecology and Obstetrics

The Genitourinary System

Technic

RADIOTHERAPY

RADIOISOTOPES

RADIATION EFFECTS—PROTECTION

ROENTGEN DIAGNOSIS

THE HEAD AND NECK

Changes in Region of Anterior Clinoid Processes Due to Expansile Tumors of Surrounding Areas. A. Tänzer. Fortschr. a. d. Geb. d. Röntgenstrahlen **94:** 85–95, January 1961. (In German) (Martinistr. 52, Hamburg-Eppendorf, Germany)

Erosions and displacement of the anterior clinoid processes may be caused by expansively growing tumors in their vicinity. The type of erosion and the direction of displacement frequently allow one to determine the position and extent of the tumor, particularly if changes can be demonstrated in neighboring parts of the skull base. The diagnostic possibilities of these alterations in the clinoid processes are illustrated in 8 case reports, and reference is made to the use of tomography. The difficulties of differential diagnosis in parasellar tumors are pointed out.

Eighteen roentgenograms. AUTHOR'S SUMMARY

Contribution to the Problem of "Cerebral Pseudotumor" and of an Intracerebral Calcification. H.-St. Meyer, G. Busch, and E. W. Dörffel. Fortschr. a. d. Geb. d. Röntgenstrahlen **94:** 107–115, January 1961. (In German) (Charité, Berlin, Germany)

For the diagnosis of cerebral pseudotumor it is postulated that a patient must have increased intracranial pressure and choked disk without evidence of a neoplasm. Furthermore, the disease should have a benign course with regression of clinical manifestations. It must not be confused with brain abscess, subdural hematoma, aneurysm, thromboangiitis obliterans, the encephalopathy of pregnancy, atypical hemicrania, exogenous poisoning, ependymitis of the aqueduct, cerebral sclerosis, cerebral manifestations of a blood dyscrasia, post-traumatic cysts, etc. The diagnosis can be made only after a true tumor has been excluded by observations over several years.

A pertinent case is reported which was followed for ten years. A nineteen-year-old girl suffered from headache, malaise, nausea and vomiting, visual disturbances, and parasthesias in the right hand. She gave a six-year history of migraine. Physical examination at that time revealed choked disks and right facial paralysis. Pneumoencephalography and Thorotrast angiography suggested a left parietal tumor, but surgical exploration was negative.

Ten years after the original study, all examinations proved negative. Only a small calcified focus had developed in the left posterior parietal area at the operative site. There was thorium storage in liver and spleen, with residual radioactivity. A diagnosis of cerebral pseudotumor is considered justified in this case, as clinical manifestations regressed without any specific therapy.

Eight roentgenograms. ERNEST KRAFT, M.D.
Northport, N. Y.

Roentgen Diagnosis of Mastoiditis in Newborn Infants and Children up to Their Second Year. V. Rajner, L. Kozelka, and V. Štěpánek. Radiol. clin. **30:** 46–51, January 1961. (In German) (Kreiskrankenhaus in Ostrava, Czechoslovakia)

For five years the authors have performed roentgen examinations of the temporal bones in infants suffering from inflammatory disease of the middle ear. They have found the studies of great help in children under two years of age, as a supplement to the clinical examination and case history.

Two hundred cases have been analyzed for this report. In 59.5 per cent of the cases pneumatization of the mastoid was good, and in 32 per cent it was rather poor; it was noted in 1 infant of two months. Correlation of the roentgenograms with the clinical features was useful in the establishment of indications for operation, especially in 7 cases of latent mastoiditis.

Six roentgenograms.

CHARLES M. NICE, JR., M.D., PH.D.
Tulane University

THE CHEST

Radiological Lung-Function Studies. R. E. Steiner, J. W. Laws, J. Gilbert, and M. J. McDonnell. Lancet **2:** 1051–1055, Nov. 12, 1960. (Hammersmith Hospital, London, W. 12, England)

The authors describe their method of studying localized changes in radiographic lung density during respiration, with simultaneous spirometric recordings. A 5-in. Philips image-intensifier is used. The electrical output of a photomultiplier in a special mounting is fed into a logarithmic amplifier and, after further linear amplification, drives one pen of a two-channel recorder. A spirometer with a variable resistor drives a second pen.

The field examined is usually a circle of 5-cm. diameter, limited by a lead diaphragm between the patient and the amplifier. The sites selected for examination are the areas immediately below the clavicles and those above the diaphragmatic domes, symmetrically on the two sides.

Good correlation was found both in timing and amplitude between respiratory and density curves. The curves obtained in normal persons are described, and the recordings obtained in 2 patients with abnormal lung conditions are analyzed. The alterations of lung density during respiration, recorded by the densitometer, are a function of the degree of expansion of the part of the lung under observation, and hence of the amount of air exchanged. Asynchronous curves imply localized air-flow obstruction.

The place of this radiological technic in the study of lung function has not yet been fully assessed. It is hoped to correlate the method with other more conventional lung-function tests to establish its clinical value as a routine procedure.

Seven figures, including 1 roentgenogram.

H. A. SWANSON, M.D.
Calgary General Hospital, Calgary, Alta.

Bronchial Carcinoma. Lobar Distribution of Lesions in 250 Cases. L. Henry Garland. California Med. **94:** 7–8, January 1961. (450 Sutter St., San Francisco 8, Calif.)

The records of 250 patients seen at the San Francisco General Hospital with microscopically verified primary carcinoma of the lung, beginning with May 1960, were reviewed to determine the lobar distribution of the tumors. The patients ranged in age from thirty-five to eighty-five years; the sex ratio was 5 males to 1 female. About two-thirds of the patients were white, the remainder were Negroes or Orientals. One hundred and

thirty-three of the tumors were located on the right side and 112 on the left. Most apparently arose in the lobar or segmental bronchi. The ratio of upper to lower lobe involvement was approximately two and a half to one.

The histologic diagnosis in this group of cases was: squamous-cell carcinoma, 33 per cent; anaplastic carcinoma, 30 per cent; adenocarcinoma, 10 per cent; alveolar carcinoma, 2 per cent; unclassified or mixed carcinoma, 25 per cent. The distribution of the lung cancers in this series is similar to that recorded by Ochsner (J. Am. Geriat. Soc. **8:** 159, 1960) in 1,453 cases.

The location of the tumors was compared to that of lobar pneumonia in young persons, as established at the San Francisco General Hospital (Heald and Coulson: California Med. **92:** 334, 1960), but no correlation was found between the location of the two diseases.

Mention is made of the fact that the majority of the tumors occurred in the lobar and segmental bronchi, rather than in the trachea and main bronchi, where Auerbach (J. Thoracic Surg. **34:** 298, 1957) found a significant incidence of "smoking" lesions (metaplasia and carcinoma *in situ*).

Two tables.

WENDELL M. BURNS, M.D.
Covina, Calif.

The Value of Periodic Mass Chest Roentgenographic Surveys in the Detection of Primary Bronchial Carcinoma in Norway. Herman Höst. Cancer **13:** 1167–1184, November-December 1960. (Norwegian Radium Hospital, Oslo, Norway)

Data are presented on 965 cases of primary bronchial carcinoma registered at the Norwegian Cancer Registry during the period Jan. 1, 1952, to July 1, 1956. About 10 per cent of the cases were detected in mass chest roentgenographic surveys. Resection was performed twice as frequently among the survey-detected cases as it was among the other cases. In the two groups, the five-year survival rate was the same, 37 per cent among the patients who had resections. There was no significant difference in the distribution of histological tumor types in the survey-detected cases as compared with the cases diagnosed on the basis of symptoms.

About 64 per cent of the 965 patients with primary bronchial carcinoma had had previous chest roentgenographic survey examinations. In 81 cases, review of earlier photofluorograms from these patients revealed changes in the region in which the tumor later manifested itself. These changes had been either overlooked or misinterpreted at the original reading or the follow-up examination.

The duration of "the silent phase" of bronchial carcinoma is discussed.

Fourteen roentgenograms; 2 graphs; 18 tables.

AUTHOR'S SUMMARY

Endobronchial Malignant Lymphoma. Report of Five Cases in Adults. Melvin L. Samuels, Clifton D. Howe, Gerald D. Dodd, Jr., Lillian M. Fuller, C. C. Shullenberger, and William L. Leary. Am. J. Roentgenol. **85:** 87–95, January 1961. (G. D. D., M. D. Anderson Hospital & Tumor Institute, Houston 25, Texas)

The authors consider endobronchial invasion a true facet of systemic lymphomatosis rather than an unusual growth variant. Seven cases presenting this complication are reported (2 in an Addendum). The clinical picture of endobronchial malignant lymphoma is suggested by a dry, irritating cough, frequently quite severe and associated with dyspnea, in a patient with an established diagnosis of the disease. This was noted in 5 of the 7 cases recorded. Hemoptysis was the initial complaint in 1 of the remaining cases and chest pain in the other. The roentgen demonstration of atelectasis (6 of the 7 cases) in such patients usually indicates the diagnosis, although other potential causes of collapse must be excluded. The atelectasis may involve the entire lung or may be lobar or segmental in distribution. Contrary to the usual opinion, detectable mediastinal lymphadenopathy need not be present nor is the pulmonary collapse often related to mechanical pressure by enlarged or matted lymph nodes.

The endobronchial lymphoma may take the form of a bulky intraluminal mass, a bronchostenosis, a granulomatous panbronchitis or peribronchitis (the most common form), or scattered plaques and nodules. The authors' cases were of the first two types.

The preferred treatment of endobronchial lymphoma is roentgen therapy. It may be employed in palliative or definitive fashion, depending on the general condition of the patient, aggressiveness of the disease, and the degree of spread. In general, the philosophy is to deliver an initial dose of sufficient magnitude that it will not be necessary to re-treat the same area at a later date. At the M. D. Anderson Hospital (Houston, Texas), it is felt that a tumor dose of 3,000 r in three to five weeks, with an additional 1,000 to 1,500 r to residual masses, when necessary, is required to achieve sterilization. When doses of this magnitude are delivered initially, there is seldom recurrence in the treated area. In cases in which the presenting pulmonary picture is dominated by the endobronchial deposits and the disease is virulent and aggressive, palliative radiation is indicated, since the prognosis for life beyond nine months to one year is poor. A tumor dose of 2,000 to 2,400 r in thirty-six to thirty-eight days has been found adequate to open the bronchus and control pulmonary symptoms. It is emphasized that these patients are seriously ill and general supportive measures are necessary. In 1 of the authors' patients, atelectasis cleared after a tumor dose of 1,000 r. In 1 patient, with unusually long survival (ten and a half years), the response to nitrogen mustard proved slightly superior to that with roentgen therapy. Nitrogen mustard has controlled respiratory symptoms in 1 of the recent cases, and radiation therapy is to be administered.

The authors urge that adequate roentgen therapy be given initially to the uncomplicated mediastinal lymphadenopathy to avoid the unfavorable complication of endobronchial invasion.

Seven roentgenograms; 1 table.

PHILIP M. JOHNSON, M.D.
Montclair, N. J.

The Stages of Pulmonary Sarcoidosis. K. Wurm. German M. Monthly **5:** 386–389, November 1960. (Höchenschwand/Schwarzwald, Germany)

On the basis of the radiological changes, pulmonary sarcoidosis has been divided into three evolutionary stages: Stage I, visceral lymph-node enlargement; Stage II, spread into the lungs; Stage III, irreversible fibrosis.

In Stage I, the involved lymph nodes are usually mediastinal, very rarely mesenteric. This is the primary stage, and manifestations in other organs never precede it. At least 40 per cent of the patients with

Stage I pulmonary sarcoidosis recover spontaneously. The author feels that cortisone treatment is unnecessary in this stage. In Stage II, lung involvement generally takes place by retrograde lymphatic spread (II *a*) against the lymph stream, just as tumors may infiltrate the lung from the hilus. Primary hematogenous extension (II *b*) is comparatively rare and leads to focal lung lesions with a different appearance and pattern. It is in the early part of Stage II that cortisone has been found to be of the most value. Roughly 40 per cent of patients with Stage II pulmonary sarcoidosis recover spontaneously. Only 20 per cent of cases go on to Stage III, clinically recognizable fibrosis. In Stage III *a*, prolifera ive changes are still going on in addition to fibrosis, and some degree of resolution can therefore be hoped for; Stage III *b* is the stage of pure fibrosis, of scarring incapable of resolution.

The stages differ not merely in degree, but in kind. Stage III does not necessarily imply a more serious condition than Stage II. Mild fibrosis may fall into Stage III, although it does not affect respiratory function or shorten the expectation of life. On the other hand, a patient with Stage II sarcoidosis may die of respiratory failure, due to dense proliferative changes throughout the whole lung.

It is emphasized that by no means every case of sarcoidosis passes through all three stages; it may become stationary or regress at any stage.

The author calls attention to the fact that in sarcoidosis, whenever there is progressive lung involvement, the mediastinal lymph nodes either cease to enlarge or actually become smaller. In Hodgkin's disease, malignant tumors, and tuberculosis this does not occur; such conditions in their advance involve lymph nodes and lungs simultaneously. This is an important differential point.

The classification has been employed in 1,000 cases of pulmonary sarcoidosis and has been found of practical value in diagnosis, treatment, and prognosis.

Two figures. RICHARD H. GREENSPAN, M.D.
Yale University School of Medicine

Tuberculosis and Asthmatic Bronchitis in Sarcoidosis. Some Observations on 150 Cases of Besnier-Boeck-Schaumann Disease. H. Ten Have and N. G. M. Orie. Dis. of Chest **39:** 42–49, January 1961. (Medical Department of the State University, Groningen, The Netherlands)

The most significant features of 150 cases of proved sarcoidosis, selected on the basis of severity from approximately 700 cases seen during the same period in The Netherlands, have been evaluated. One of the most striking observations was the rather high frequency with which tuberculosis was encountered in the family history (34 per cent). Tubercle bacilli were demonstrated in 11 patients during the course of the study. Fourteen patients had manifest and 21 dubious calcifications. A second important observation was the frequent occurrence of asthmatic and other "allergic" conditions both in the patient and in his family.

The radiological course of the disease could be studied in 146 patients; in the remaining 4 the changes on the roentgenogram were too slight to warrant a diagnosis Forty-nine patients had only lymph-node enlargement and 68 had only peripheral lesions. The "asthma" component of sarcoidosis was especially manifest in the latter group (43.7 per cent) and was about twice as common in the men as in the women. In 33 per cent of the patients the radiological abnormalities had completely or almost completely disappeared after a period averaging twenty-six months. Marked enlargement of the lymph nodes was more frequent in women than in men; peripheral pulmonary changes were more predominant among the men.

In Stage I (lymph node involvement only), the percentage of cures was more or less the same. In the second stage (initial dissemination), the men had a considerably better chance for recovery than women, while in the third stage (peripheral lesions) the reverse was true (24 per cent in women; 14 per cent in men). In patients with erythema nodosum, the prognosis was particularly good, while in those with iridocyclitis and in those with skin lesions, it was poor.

Treatment with ACTH and corticosteroids had a favorable effect on both the "asthmatic" factor and on the anatomical changes.

Serious sequelae occurred in 6 to 10 per cent of the cases, and the mortality rate was 2 per cent (overall figure based on the entire group of 700 cases).

One table. H. N. STURTEVANT, M.D.
Springfield, Mo

A Three-Step Method for the Diagnosis of Solitary Pulmonary Nodules. L. Henry Garland. Canad. M. A. J. **83:** 1079–1082, Nov. 19, 1960. (450 Sutter St., San Francisco 8, Calif.)

A three-step method is described for the preoperative or nonsurgical diagnosis of solitary pulmonary nodules. It consists essentially in a thorough roentgen *examination* at the patient's first visit, brief *clinical* review, and pertinent *laboratory* studies.

The roentgen examination should be completed by stereoscopic postero-anterior, or oblique, or lateral projections, depending on the location of the opacity. Posterior lordotic views, heavy-density views, tomograms, and fluoroscopy should be employed as indicated. Sharpness of margin, calcification, and the presence of adjacent infiltration should all be taken into consideration. Any change in size of the lesion from previous roentgenograms should be noted. Fluoroscopy permits rapid detection of vascular malformations.

Clinically, the four important points are the patient's age, sex, the presence or absence of thoracic symptoms, and the history of recent tap or surgery. Inquiry should be made concerning the use of oily nose drops, since lipid pneumonia may present as a solitary nodule.

Skin tests and sputum studies are of limited value in the identification of solitary pulmonary nodules, but in persons under forty years of age, they have at times proved helpful.

With the three-step method, it was possible to classify as presumptively "benign" or "malignant" 106 of 115 consecutive pulmonary nodules. In the entire group, there were 74 benign lesions, 66 of which were correctly classified by the three-step method (89 per cent). Malignant lesions numbered 41, 34 of which were so diagnosed (83 per cent). ZAC F. ENDRESS, M.D.
Bloomfield Hills, Mich.

Right Supernumerary Internal Bronchus or "Accessory Cardiac Bronchial Stump." Cine-Endoscopic and Bronchographic Documentation. J. Ioannou and B. Gamain. J. franç. de méd. et chir. thorac. **15:** 15–18, January 1961. (In French) (Clinique de pneumophtisiologie, Paris, France)

Three cases are presented in which an abnormal su-

supernumerary bronchial stump was found on the mediastinal surface of the bronchus intermedius. In each instance the bronchus was limited by a cartilaginous spur.

Three bronchograms.

CHARLES M. NICE, JR., M.D., PH.D.
Tulane University

Pleuro-Pulmonary Manifestations of Systemic Lupus Erythematosus. Donato Alarcón-Segovia and Donato G. Alarcón. Dis. of Chest **39:** 7–17, January 1961. (Hospital de Enfermedades de la Nutrición, México, D.F.)

The authors discuss the pleuropulmonary lesions occurring in 48 proved cases of systemic lupus erythematosus. Thirty-eight patients (79 per cent) in this group had clinical or radiological manifestations of respiratory involvement during the course of the disease; only renal involvement was encountered more frequently. Three fundamental radiologic patterns were found in the pulmonary parenchyma: (1) a fine micronodular infiltrate, (2) a diffuse infiltrate resembling pneumonitis, and (3) linear shadows of atelectasis, characteristically located in the lower lobes. Pleural effusion was evident on the chest roentgenogram of 21 patients and was large enough to be detected clinically in 11. A dry pleuritis was found in 1 patient. The astonishing migratory character of the infiltrates and the fact that, despite the impressive roentgen picture, physical findings are scarce are emphasized. No satisfactory explanation for the migratory tendency of the pulmonary infiltrates has been given; although systemic lupus erythematosus may exhibit spontaneous remissions, migration does not follow them nor is it the result of treatment. In spite of their high frequency, the pleuropulmonary lesions are not pathognomonic for the disease. Nineteen cases in the present series came to autopsy; histologic and clinical findings could not be correlated. Specific lesions in the lungs were found in only 3 cases.

Ten roentgenograms; 7 tables.

H. N. STURTEVANT, M.D.
Springfield, Mo.

Diffuse Pleural Mesotheliomas in South Africa. C. A. Sleggs, Paul Marchand, and J. C. Wagner. South African M. J. **35:** 28–34, Jan. 14, 1961. (West End Hospital, Kimberley, Union of South Africa)

Diffuse pleural mesothelioma is generally considered a rare tumor. The authors, however, present the clinical and radiological findings in 34 patients with histologically proved mesothelioma from a larger series of 41 cases, most of which were encountered in the past four years. Thirty-three of the 34 patients gave a history of exposure to crocidolite asbestos. Nineteen worked with asbestos and all but 2 of the other 15 patients were either born or had spent a significant period of their lives in the asbestos area of the northwestern Cape Province of South Africa. Asbestos bodies were found in the lung tissues of 30 per cent of the cases.

In the present series, the latent period, between first apparent exposure to asbestos dust and the initial symptoms of the disease, was between twenty and sixty years; a long latent period between initial exposure and malignant development is considered a feature of occupational tumors.

Most of the patients were over forty years of age. Twenty-four were men and 10 were women. The majority presented with symptoms suggestive of a primary tuberculous effusion. Clinically, mesothelioma may be described as showing three stages: (1) pleurisy and bronchitis, which may be alleviated by antibiotics; (2) pleural effusion and pleural thickening, usually leading to hospital admission; (3) obvious malignant thoracic tumor.

In the early stages, auscultatory evidence of pleurisy, bronchitis, or consolidation is usual. As the disease progresses, respiratory excursions diminish until eventually a "frozen chest" results. The chest is then stony-dull to percussion. During the late stage, signs of secondary spread may appear. The peritoneum is usually infiltrated by direct extension through the diaphragm. The liver may be enlarged and nodular, due to perihepatic involvement. Localized masses due to disease of the omentum or para-aortic lymph nodes may be felt. In these cases ascites is common. Hematogenous spread is unusual, and in only 2 of the authors' cases did distant metastases develop.

The radiologic findings roughly parallel the clinical course of the disease. In about a third of the cases, evidence of asbestosis was present on the initial radiograph. In a well established case, the appearance may be that of a generalized homogeneous clouding of the lung fields, particularly the lower zones, or a fine striate and fibrillary change in the lung structure, with progressive loss of pulmonary radiolucency. In the majority of cases of asbestosis, old pleuritic changes were also seen, in the form of bilateral thickening, adhesions, and rather characteristic dense calcific plaques. While pleural thickening *per se* in asbestosis is non-specific in character, sclerotic pleurisy with plaque formation constitutes a "readily recognizable and rather typical entity. The pattern of calcification patently differs from pleural calcification due to other causes." The plaques may be few or widespread; they are usually bilateral and disposed in irregular patches, chiefly in the middle and lower zones. Seen end-on they appear as linear plaques in the periphery, along the diaphragmatic contours, and adjacent to the mediastinum.

In the majority of cases, no evidence of preceding pleural or pulmonary asbestosis was found. These cases invariably showed unilateral involvement in the form of diffuse thickening or effusion. The appearance may be massive from the beginning, but usually a localized scalloping or solitary mass in the periphery raises the first suspicion of pleural neoplasm. As the disease advances, more extensive nodular or "lumpy" pleural thickening develops. This pattern of unilateral pleural pathology, in a patient from the asbestos area, is a highly significant finding, but a similar appearance may be produced by secondary malignant involvement of the pleura. Very often a large pleural effusion will obliterate the picture and only after removal of the fluid does it become apparent that the pleura is grossly thickened and nodular. An induced pneumothorax will clearly demonstrate the rather characteristic pattern of marginal massive nodularity along the parietal chest wall, over the surface of the collapsed lung, and at the base. Eventually the pericardium is involved by direct extension, and the resulting effusion causes progressive enlargement of the cardiac silhouette and a change in its configuration. Occasionally, extrapleural extension occurs, with radiological evidence of rib destruction.

In 27 of the authors' 34 cases, the mesothelioma was located on the right. This right-sided preponderance

has been noted by others. In no instance was the mesothelioma tous process initially bilateral, although roentgenography in 10 patients revealed bilateral changes due to asbestosis.

The information obtained from thoracoscopy has been disappointing and, in so far as possible, a specimen is obtained at open operation for histologic examination.

There is no satisfactory treatment for pleural mesothelioma, and the prognosis is extremely poor. Of the 34 patients in the present series, 28 have died, 17 within a year of the development of symptoms. Four patients with seemingly localized areas of disease were given deep x-ray therapy; all were dead within a year. Radioactive gold was instilled intrapleurally in 6 patients; 4 died within thirteen months; 2, treated recently, were still alive at the time of writing. The authors advise this form of therapy for the comparatively early case, while the lung is relatively elastic.

Four roentgenograms [which do not demonstrate the points under discussion particularly well].

JAMES W. BARBER, M.D.
Cheyenne, Wyo.

Slowly Expanding Intrapleural Lesion Due to a Foreign Body. Report of a Case. John S. Trombold, Alvin C. McCuistion, and H. William Harris. New England J. Med. **264:** 172–174, Jan. 26, 1961. (University of Utah College of Medicine, Salt Lake City, Utah)

The authors report the case of a patient with a slowly expanding intrapleural mass which at operation proved to be due to a retained surgical sponge. In 1945, thoracotomy was performed to remove a bullet. Although the patient had few symptoms, roentgenograms taken over the next fourteen years revealed a slowly expanding homogeneous mass at the periphery of the right lung. Before the second thoracotomy, the abnormality was believed to be related to the old thoracic bullet wound; lymphocele, arterial aneurysm, neuroma, and loculated pleural effusion were regarded as possible explanations. The cause of the progressive enlargement of the mass in this case is not known; it may have been due to fibrosis caused by the gradual breakdown of the sponge and local dissemination of the fibers, to recurrent hemorrhage into the mass, or to chronic infection.

Three roentgenograms; 1 photograph.

H. N. STURTEVANT, M.D.
Springfield, Mo.

Neurogenous Neoplasms of the Mediastinum. Harold A. Oberman and Murray R. Abell. Cancer **13:** 882–898, September-October 1960. (University of Michigan Medical School, Ann Arbor, Mich.)

The findings in 62 neurogenous neoplasms of the mediastinum are reported. Thirty-eight of the tumors were of nerve sheath origin and 24 arose from the sympathetic nervous system. All but 3 were located in the posterior mediastinum, principally in the costovertebral gutter. Nine (14 per cent) were histologically malignant.

Twenty-nine of the 38 nerve sheath tumors were neurilemmomas, 5 were neurofibromas, and 4 were neurogenous sarcomas. The majority of neurilemmomas were detected incidentally during routine roentgenologic surveys of the chest. Neurofibromas were found in younger patients than were the other nerve-sheath neoplasms and, as would be expected, they tended to occur multicentrically. The other tumors in this series were solitary. The 5 patients with neurofibroma had stigmata of von Recklinghausen's disease, including subcutaneous tumors and *café au lait* spots. The neurogenous sarcomas were larger and tended to occur in a more advanced age group than did the benign nerve-sheath tumors; the majority produced symptoms by virtue of their great size.

The sympathetic neurogenous tumors included 19 ganglioneuromas (14 mature, 5 partially differentiated), 2 sympathicoblastomas, and 3 sympathicogoniomas. These neoplasms occurred in much younger patients than those of nerve-sheath origin, and there appeared to be an increase in the maturity of the neoplasm with the increasing age of the patient. They tended to be larger than their nerve-sheath counterparts and more frequently exhibited "dumbbell" growth into the intervertebral foramina. They occurred at all levels of the posterior mediastinum.

The histopathology of mediastinal neurogenous neoplasms is reviewed and correlated with the prognosis

Twenty-three figures; 4 tables.

H. N. STURTEVANT, M.D.
Springfield, Mo.

THE HEART AND BLOOD VESSELS

Idiopathic Hypertrophic Subaortic Stenosis. Clinical, Hemodynamic and Angiographic Manifestations. Eugene Braunwald, Andrew G. Morrow, William P. Cornell, Maurice M. Aygen, and Theodore F. Hilbish. Am. J. Med. **29:** 924–945, December 1960. (National Institutes of Health, Bethesda, Md.)

Fourteen cases are reported in which a diagnosis of idiopathic hypertrophic subaortic stenosis, *i.e.*, left ventricular hypertrophy producing severe obstruction to left ventricular outflow, was established. All 14 patients had systolic murmurs, most prominent either at the mitral or tricuspid areas. Left ventricular systole was prolonged, resulting in paradoxical splitting of the second heart sound. Electrocardiograms showed either left ventricular hypertrophy or anomalous atrioventricular excitation. Roentgen examination demonstrated left atrial and ventricular enlargement without aortic dilatation. Left heart catheterization revealed systolic pressure gradients within the ventricle ranging from 40 to 185 mm. Hg, and localized the site of obstruction to the left ventricular outflow tract in each instance. The left ventricular pressure pulses exhibited a characteristic notch in early ventricular systole, and a striking rise during atrial contraction. Both the palpable and recorded peripheral arterial pressure pulses rose rapidly during early systole, unlike those in valvular aortic stenosis. Left ventricular angiocardiography disclosed a markedly thickened ventricular wall obstructing the outflow tract of the left ventricle only during a portion of the cardiac cycle.

At open operation the angiocardiographic interpretations were confirmed in 5 patients; in 2, the hypertrophied muscular ring was incised longitudinally to relieve the obstruction and the early clinical and hemodynamic results of this procedure have been encouraging.

With the delineation of its clinical, hemodynamic, angiocardiographic, and anatomic features, idiopathic hypertrophic subaortic stenosis emerges as a specific entity which can be distinguished preoperatively from discrete valvular and subvalvular stenosis. Its recognition is important in selecting for operation patients

with all forms of obstruction to left ventricular outflow and in planning the surgical procedure.

Twenty-three roentgenograms; electrocardiograms, phonocardiograms, and pressure recordings.

AUTHORS' SUMMARY

Aortography by Catheterization of the Right Atrium. A Safe and Reliable Method. Alfonso Zerbi-Ortiz and William V. Weldon. New England J. Med. **264:** 19-23, Jan. 5, 1961. (Walter Reed General Hospital, Washington, D. C.)

The authors describe the method of opacification of the thoracoabdominal aorta and its major branches now employed at the Walter Reed General Hospital (Washington, D. C.). It is a modification of the technics of Bernstein *et al.* (Surgery **44:** 529, 1958) and Steinberg *et al.* (Am. J. Roentgenol. **82:** 758, 1959. Abst. in Radiology **75:** 494, 1960) and represents an extension of regional angiocardiography. The major difference between this and the intravenous method is that a cardiac chamber is utilized as the site of injection. This permits the delivery of a large quantity of concentrated contrast material by a mechanical injector in one and a half to three seconds.

Under local anesthesia, a catheter is placed in a peripheral vein and advanced into the middle of the right atrium under fluoroscopic control. A preliminary injection of sodium dehydrocholate (Decholin) and 90 per cent sodium diatrizoate (Hypaque) is made to determine the circulation time and sensitivity to the contrast medium. With a compressed-air injector, the contrast material, 1.2 ml. sodium diatrizoate per kilogram of body weight, is injected and serial roentgenograms are obtained in one or two planes at a rate of one per one and a half seconds, bracketing the circulation time for a period of twenty to twenty-five seconds. A portable x-ray unit may be utilized to obtain a roentgenogram of areas of secondary interest. Constant electrocardiographic monitoring is carried out during the procedure.

This method of antegrade aortography has been employed in 50 patients. In each case the study was of satisfactory diagnostic quality, and no complications were encountered other than an intense flush and a sensation of heat. In the authors' experience, the method has proved most useful in preoperative and postoperative diagnosis and evaluation of patients with known or suspected aortic aneurysms, congenital lesions of the aortic arch, hypertension of suspected renal origin, and occlusive disease of the aorta and the iliac, renal, carotid, vertebral, and subclavian arteries.

Seven roentgenograms; 1 pressure tracing.

MORTIMER R. CAMIEL, M.D.
Brooklyn, N. Y.

Roentgen Diagnosis of Caval Thrombosis. J. Pfeiffer and R. Barke. Fortschr. a. d. Geb. d. Röntgenstrahlen **93:** 594–597, November 1960. (In German) (Karl-Marx-Universität, Leipzig, Germany)

The diagnosis of thrombosis of the inferior vena cava is easily established by the visible varicose widening of the collateral veins, but the site of the occlusion and its extent are not definite. Numerous methods employed in the last ten years for the radiographic demonstration of the veins have the disadvantages that only a small portion of the venous network is shown and that the contrast filling of the vena cava is usually incomplete due to the dilution by blood from the other side of the body. The authors describe the technic of cavography introduced by Helander and Lindbom (Acta radiol. **45:** 289, 1956. Abst. in Radiology **68:** 288, 1957) who were interested primarily in the determination of retroperitoneal tumors and actually demonstrated a 3-cm. lymph node metastasis which compressed the vena cava. The procedure consists of (1) bilateral puncture of the femoral veins; (2) introduction of Seldinger's catheters; (3) injection of contrast material with moderate pressure; (4) short interval serial films. A case is reported in which complete occlusion of the inferior vena cava was shown by this method.

Three roentgenograms; 1 diagram.

ILONA D. SCOTT, M.D.
Lewisburg, W. Va.

Measurement of the Pressure in the Right Coronary Artery. H. Fiehring and M. Thurm-Wagner. Fortschr. a. d. Geb. d. Röntgenstrahlen **93:** 582–584, November 1960. (In German) (M. T.-W., Röntgen- und Radiuminstitut der Medizinischen Akademie Erfurt, Germany)

Malamos and his co-workers (Ztschr. f. Kreislaufforsch. **49:** 58, 1960) found that, in catheterization of the coronary vessels of the dog, an aortic pressure curve was registered only in the central portion of the coronary artery; toward the periphery the form of the curve resembled that of the ventricle, and with the catheter in an extreme peripheral position, with occlusion of the lumen of the artery, no pressure changes were seen. The curve in the mid region of the coronary artery was thought to be a mixed form between the aortic and ventricular pressures. Results in man were inconclusive because of extrasystoles.

Because of a suspected supravalvular aortic stenosis, a 15-year-old girl was catheterized *via* the brachial artery. The registered curve, in the plane where the aortic valve was assumed to be, was thought to represent the toned-down ventricle pressure curve. A few cubic centimeters of contrast material were injected and the catheter was seen to be in the right coronary artery. Except for a few extrasystoles and some flattening of the T-waves, there were no complications

This observation of the authors confirms that of Malamos *et al*, that in man the pressure curve of the coronary arteries resembles that of the ventricle. Caution is recommended in the retrograde catheterization of the left ventricle, since the pressure curve is not proof of the catheter localization.

One roentgenogram; 2 pressure curves.

ILONA D. SCOTT, M. D.
Lewisburg, W. Va.

Robot Angiography. A Preliminary Report. J. A. Veiga-Pires and B. E. Godfrey. Lancet **2:** 542–544, Sept. 3, 1960. (Royal Northern Hospital, Holloway, London, N. 7, England)

This communication reports work designed to answer the need for (1) accurate timing of the radiographic exposures in peripheral arteriography and (2) reduction of the dose of radiation to the radiologist, the staff, and the patient. The procedure described uses a Geiger counter to detect the arrival of radioactive sodium which is mixed with the contrast medium. It is essentially the same as that described by Greenspan *et al.* (Am. J. Roentgenol. **83:** 1034, 1960. Abst. in Radiology **76:** 667, 1961) except that the latter authors

used I^{131}. The chief value of the method is to demonstrate the distal arteries in the lower limbs. It is estimated that the radiation dose to a patient at the center of the trunk per injection of 50 μC of Na^{24} is of the order 90 mrad, with the gonad dose probably less than this. With current arteriographic technics, involving repeated exposures, the gonad dose is of the order of 1,500 mrad for 15 exposures in males. For the patient, a small gonad dose from x-ray exposures will be saved at the expense of an additional γ-ray dose of the order of 5 per cent of the total x-ray exposure. For the staff, the reduced number of exposures will offer appreciable protection.

Two roentgenograms; 1 drawing.

THE DIGESTIVE SYSTEM

Non-Collapsing Air-Filled Esophagus in Diseased and Postoperative Chests. Gunnar Blomquist and Paul S. Mahoney. Acta radiol. **55:** 32–42, January 1961. (University Hospital, Lund, Sweden)

The esophagus is a self-collapsing organ which normally does not contain air. If, however, its walls become fixed by scarring and adhesions to surrounding structures, it may remain patent and fail to collapse, being demonstrable roentgenographically as a vertical, linear, air-filled structure about 1 cm. in diameter, which is often curved, kinked, and deviated to one side of the chest. Anatomically, the esophagus is well anchored in its upper third, but relatively mobile in its lower two-thirds; therefore deviation is usually greater in the distal portion.

Because the esophagus extends from the thoracic inlet to the diaphragm, it presents a rather large surface area to a great number of anatomic structures and consequently is prone to involvement in any pathologic process arising in adjacent structures. The esophageal wall may also become rigid and fail to collapse in some intrinsic conditions, *e.g.*, scleroderma, achalasia, and scirrhous carcinoma.

The air-filled esophagus must be differentiated from other air-containing structures such as loculated effusions, abscess cavities, lung herniations, and cysts. Three roentgen features which are of importance in identifying the esophagus are: (1) the often characteristic, vertical, linear, and tortuous shape of the structure; (2) the absence of a fluid level; (3) delineation with barium.

Ten illustrative cases are reported briefly.

Twenty roentgenograms.

CAPT. ROBERT E. WILDIN, M.C.
Lackland AFB, Texas

Haematemesis and Melaena. Their Early Radiological Investigation. G. N. Chandler, A. D. Cameron, A. H. Nunn, and D. F. Street. Lancet **2:** 507–510, Sept. 3, 1960. (Central Middlesex Hospital, London, N.W. 10, England)

At the Central Middlesex Hospital (London) early radiologic examination of patients admitted with hematemesis and/or melena is a part of a combined investigation which also includes estimation of nocturnal gastric acidity and gastroscopy. The examination is undertaken in the ward on the day after admission. Food and fluids are withheld for only two hours. The patient wears a close-fitting gown with few tapes and lies on a cloth-covered board, about 26 × 14-in., since sagging of the normal hospital mattress makes accurate positioning impossible. After drinking 4 oz. of barium suspension, the patient is immediately placed in the right lateral position with a 12 × 10-in. cassette and grid between him and the board. An exposure is made in this position, followed as rapidly as possible by further roentgenograms in the right anterior oblique, right posterior oblique, and anteroposterior projections. The portable x-ray machine used has an output of 30 ma at 85 kvp; exposure times vary from one to two seconds, depending on the build of the patient and the projection employed.

One hundred and fifty patients have been investigated by this technic in the acute stage of bleeding. In 83 per cent the cause of the bleeding was correctly diagnosed, as established by a later barium-meal examination, at operation, or at necropsy. The results indicate that in most instances information of diagnostic value is provided by the bedside investigation. No complications were encountered. In no instance was further bleeding attributed to the procedure, and the barium did not cause intestinal obstruction in any patient in whom the radiologic examination shortly preceded emergency partial gastrectomy.

Five roentgenograms; 3 tables.

Emergency Upper Gastrointestinal Examination During Hematemesis. R. Fontaine, P. Warter, and F. Weill. Ann. de radiol. **4** (nos. 1–2): 87–99, 1961. (In French) (Clinique chirurgicale A de Strasbourg, France)

An analysis of 910 emergency upper gastrointestinal examinations during hematemesis, reported by various authors, was made. It was concluded that three or more of the following criteria must be positive in order to consider a case of hematemesis severe: (1) sudden syncope; (2) a drop of 52 mm. or more in the blood pressure; (3) the presence of tarry stools on three occasions within twelve hours; (4) hematemesis of a half liter or more; (5) a drop in the red blood cell count to under three million.

The emergency upper gastrointestinal examination does not constitute a serious danger to the patient, even when performed during the early period of hematemesis. The decubitus position with a 45° tilt of the examining table is most often used, with lateral or oblique decubitus when location of the gastrointestinal lesion is required.

Shortcomings and difficulties of performing and interpreting the examination were studied. Posterior and superficial ulcerations were the most difficult to demonstrate, along with esophageal varices. Hence, routine splenoportography is recommended as a complement to the barium swallow.

The sooner the upper gastrointestinal examination was carried out after the onset of hematemesis, the better was the demonstration of the lesion, because of local vasomotor phenomena that are most manifest early in the course of bleeding. According to Schatzki and Blade (New England J. Med. **259:** 910, 1958. Abst. in Radiology **74:** 329, 1960), the etiology of 50 per cent of the cases of upper gastrointestinal bleeding will remain obscure if the examination is not performed promptly. Overall results during early examination were 85 per cent positive; the incidence of false-positive or false-negative results was in the range of 10 per cent.

Fourteen roentgenograms; 10 diagrams; 7 tables.

PETER TORBEY, M.D.
University of Washington School of Medicine

The Dumping Syndrome: Clinical and Radiological Aspects. H. T. Cox and W. R. Allan. Lancet **2:** 1261–1263, Dec. 10, 1960. (Withington Hospitals, Manchester, England)

A study was made of dumping attacks in 500 patients who had had an elective gastric operation in the past six years, with particular attention to the clinical aspects of the attacks and to the radiological picture during their course.

Dumping after subtotal gastrectomy may be brought on by eating specific foods, as milk, mild puddings, eggs, fats, chocolate, and pastries. The outstanding symptoms of an attack are profound weakness and a feeling of light-headedness. The patient may be totally incapacitated. Walking, especially in a warm atmosphere, and ingestion of hot foods increases the severity of the attack.

The authors employed specific foods to induce dumping and then performed radiologic examinations during and after the attacks. During the attack there was complete stasis and dilatation affecting the gastric remnant, duodenum, and jejunum, with absence of peristalsis. The appearance and disappearance of these changes coincided with the beginning and ending of the episode. The worse the attack, the more striking were the changes demonstrated.

The authors' findings differ from those of previous workers, who used a 50 per cent glucose solution to produce dumping, in two essential points—the absence of motor activity and the lack of evidence of increased fluid in the gut during the attack.

Two roentgenograms. H. A. SWANSON, M.D.
Calgary General Hospital, Calgary, Alta.

Gastrectomy and the Blind-Loop Syndrome. V. J. Kinsella and W. B. Hennessy. Lancet **2:** 1205–1209, Dec. 3, 1960. (St. Vincent's Hospital, Sydney, Australia)

The authors review the various causes that have been advanced for the dumping syndrome. In their experience, dumping and diarrhea are not primarily and essentially caused by: (1) altered time-relationships with failure to mix; (2) large stoma; (3) loss of this or that fraction of the stomach; (4) loss of hopper function; (5) loss of digestive secretions; or (6) precipitate emptying into the efferent loop. They believe that patients with the dumping syndrome have only one factor in common, *i.e.*, stasis in the duodenojejunal loop. Seven illustrative cases are reported.

After a properly constructed gastrectomy, roentgen examination should reveal the barium passing easily and freely into the efferent jejunal loop. The afferent loop should show, at most, a slight trickle of barium gradually tailing off before the second part of the duodenum is reached, just enough to demonstrate that there is neither obstruction at the critical point near the lesser curvature nor any dilatation of the loop.

Patients suffering from afferent-loop stasis fall into three radiologic groups:

1. In the first group there may be no radiologic signs, because the stasis is caused by obstruction at the point where the afferent loop meets the stomach and barium is therefore prevented from outlining the obstructed loop.

2. In some patients the obstruction is at a point slightly proximal to the stoma; this is shown when the barium passes freely back into the afferent loop for one or two inches and then stops abruptly.

3. In other patients, the stasis is caused by free retrograde emptying of the stomach into the afferent loop, and then emptying of the afferent loop into the stomach, so that a pendulum movement results.

Nonfilling of the afferent loop may therefore be associated with a perfectly constructed anastomosis or with a seriously obstructed loop. If the patient suffers from malabsorption, it is advisable to perform choledochography in the hope that the duodenum may be demonstrated.

The causes of afferent-loop stasis are discussed, and the technical details of avoiding it are described. A first principle of gastrointestinal surgery is that an end-to-side anastomosis must achieve a quiet confluence of unobstructed streams.

Six roentgenograms; 1 drawing.

H. A. SWANSON, M.D.
Calgary General Hospital, Calgary, Alta.

Juvenile Gastric Cancer. E. de Arzua Zulaica, J. L. Obregon Icaza, and J. Gonzalez del Tanago. Rev. clín. españ. **80:** 45–50, Jan. 15, 1961. (In Spanish) (Bilbao, Spain)

This is a report of a gastric carcinoma occurring in a 19-year-old female, who also had a benign gastric ulcer which disappeared under treatment. When the patient was seen initially, antral stiffening was observed which was thought to represent reaction from the ulcer. After treatment and disappearance of the ulcer and symptoms, antral wall rigidity was again observed on repeated examinations. Surgery revealed a neoplasm without metastasis or adenopathy.

The authors briefly review the literature and point out that radiologists are prone to carry out stomach examinations under a false sense of security in younger patients. They also call attention to the frequent coincidence of gastric and ovarian cancer and urge that in all cases of ovarian cancer the stomach be explored, and vice versa.

Twenty roentgenograms; 2 photographs; 3 photomicrographs. DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Roentgenology of Gastric Sarcoma. B. Kisseler and P. Thurn. Fortschr. a. d. Geb. d. Röntgenstrahlen **94:** 14–30, January 1961. (In German) (Medizinische Universitätsklinik, Bonn, Germany)

Gastric cancer is rare, constituting only 1 to 2 per cent of all cancers of the stomach. It occurs for the most part in middle-aged men. Since it is radiosensitive and the cure rate is high, an early diagnosis is essential.

The following forms of lymphosarcoma and reticulum-cell sarcoma are recognized: (1) circumscribed (exogastric and endogastric), (2) diffuse, and (3) transitional. The circumscribed exogastric form has a tendency toward ulcer formation. It must be differentiated from uncomplicated ulcer, tumors of the left lobe of the liver, and retroperitoneal sarcoma. Pneumoretroperitoneum is of diagnostic value, but only as long as widespread adhesions are absent. The rare circumscribed endogastric sarcoma is found usually at the greater curvature side of the stomach. As the tumor enlarges, surface ulcerations develop in most instances. Differential diagnosis includes gastric carcinoma, myoma, fibroma, and lipoma.

The diffuse form of lymphosarcoma and reticulum-cell sarcoma is localized predominantly in the gastric

fundus and corpus. It may simulate rugal thickening and infiltrating carcinoma. The esophagus remains normal, as does the cardia. Associated enlargement of the spleen may serve as a diagnostic clue. Lymphogranulomatosis and aleukemic lymphadenosis must be considered in the differential diagnosis, although they can be excluded clinically. The diffuse intramural form causes giant rugae and multiple ulcerations.

The radiological signs of lymphosarcoma and reticulosarcoma are described with reference to 9 cases which were proved by biopsy or autopsy. Metastatic lesions in liver, pancreas, spleen, and/or lymph nodes were found in all. An analysis of the findings shows that a probable preoperative diagnosis may be made in a number of cases.

Postoperatively, survivals have been observed for periods of five to twenty-two years. Radiation therapy has also been instrumental in prolonging life, especially when it follows subtotal gastrectomy.

Fifteen roentgenograms; 2 photographs.

ERNEST KRAFT, M.D.
Northport, N. Y.

Accessory Splenic Tissue Producing Indentation of the Gastric Fundus Resembling Gastric Neoplasm. T. K. Das Gupta and R. C. Busch. New England J. Med. **263:** 1360–1361, Dec. 29, 1960. (Mt. Sinai Hospital, Chicago, Ill.)

The authors report a case in which an accessory spleen at the tip of the tail of the pancreas produced a filling defect in the fundus of the stomach near the esophagocardiac junction which could not be distinguished from an intragastric neoplasm. The patient had undergone splenectomy several years previously. Her chief complaint was severe epigastric pain accompanied by nausea and vomiting. At operation, the accessory splenic tissue in the tail of the pancreas was found and resected. The patient is now asymptomatic.

One roentgenogram; 1 drawing.

ZAC F. ENDRESS, M.D.
Bloomfield Hills, Mich.

Tuberculosis of the Duodenum. John S. Jachna, Hyman Peck, and James G. Davis. California Med. **94:** 37–39, January 1961. (Wadsworth Hospital, VA Center, Los Angeles 25, Calif.)

A case is reported of ulcerative tuberculosis of the second portion of the duodenum, with radiographic findings. Roentgenographically the lesion simulated both neoplasm and postbulbar ulceration of the duodenum. At operation it resembled a neoplasm. At autopsy, tuberculosis of the second portion was observed, with postsurgical changes and caseous tuberculous lymphadenitis of paraduodenal, gastrohepatic, and porta hepatis nodes. Generalized peritonitis, pulmonary embolism, and focal hemorrhagic pancreatitis were also noted.

In roentgen studies of duodenal tuberculosis, the mucosa is usually irregular over a long segment, often with polypoid changes suggesting neoplasm, and may or may not be ulcerated. In some cases where the duodenal bulb is involved, the deformity is difficult to differentiate from a duodenal ulcer. A delay of passage of barium through the involved area of duodenum, with dilatation both proximal and distal to the lesion, is occasionally seen. Sinus tracts leading from the ulceration can be observed. As the lesion heals, scarring can occur and with it the development of obstruction by stenosis, angulation, or retraction of the bowel by adhesive bands.

Three roentgenograms; 2 photomicrographs.

WENDELL M. BURNS, M.D.
Covina, Calif.

Roentgen Diagnosis of Pancreatic Disease. Newer Methods. Robert D. Moseley, Jr. Arch. Int. Med. **107:** 31–36, January 1961. (950 E. 59th St., Chicago 37, Ill.)

The author discusses the various radiological technics for the diagnosis of diseases of the pancreas, beginning with the one most commonly employed—the gastroduodenal examination. Because localization of masses depends on the types of extrinsic deformity of the gastrointestinal tract, the accuracy of this method is not high. The standard signs—widening of the duodenal loop, the "reverse 3 sign" in the second portion of the duodenum, and an impression in the duodenal bulb resulting from a dilated common duct, particularly associated with mucosal abnormalities in the second portion of the duodenum—are difficult to evaluate, often occur late in the course of the disease, or are infrequently encountered. An accumulation of gas in a segment of the small bowel, a localized adynamic ileus, is frequently associated with acute pancreatitis. Unfortunately the borderland between normal and abnormal is very indistinct, and the roentgen findings alone will not support a diagnosis. Demonstration of calculi within the parenchyma and ducts is, of course, diagnostic of chronic calcareous pancreatitis.

Operative pancreatography by the transduodenal route is the nearest approach to direct visualization of the pancreas; it is technically difficult, however, and since it is an operative procedure, its usefulness is limited. Angiography of the pancreatic vessels has not been practically realized. The technic of pneumoretroperitoneal pancreatography, in which the stomach and duodenum are opacified with orally administered organic iodine compounds, the biliary and urinary tracts visualized with intravenously administered medium, and the retroperitoneal potential space filled with carbon dioxide, makes it possible in many instances to outline the pancreas and to detect lesions producing an increase in size of this organ. Body-section roentgenography is an important adjunct to this procedure. Since the gallbladder usually does not opacify in the presence of acute cholecystitis, intravenous cholangiography may be of value but is not infallible in differentiating acute cholecystitis and pancreatitis. Percutaneous direct cholangiography by the transhepatic route is of limited usefulness because of the danger of bile peritonitis. Splenoportography may be employed in estimating the retroperitoneal invasiveness of pancreatic neoplasm and for evaluation of operability.

Many substances for direct visualization of the pancreas are currently under investigation. Until such compounds are available for clinical use, the radiologic diagnosis of pancreatic disease must rest on the indirect methods mentioned above.

Thirteen roentgenograms.

WILLIAM H. ELLSWOOD, M.D.
Charleston, W. Va.

Roentgenologic Determination of the Liver Volume. L. Walk. Acta radiol. **55:** 49–56, January 1961. (Central Hospital, Eskilstuna, Sweden)

The size of the liver, estimated by clinical palpation,

differs considerably from that found at autopsy, and the palpability varies from case to case and is difficult to evaluate. A roentgen method of volume determination is described in this article. The error is said to be less than ±16 per cent in the majority of cases, although occasionally it may be as much as 27 per cent, the actual volume being smaller than calculated.

The liver, as viewed on films, is measured in three diameters, corrected as to actual size: (A) from the right border to the middle of the left cupola of the diaphragm; (B) from the anterior border to the most distal part of the posterior surface as outlined by the diaphragm; (C) from the lower surface of the liver, where it lies close to the upper pole of the kidney, in a transverse direction through the body of the liver to its upper surface at the lateral part of the diaphragm. The product of these three measurements divided by an index number (based on the configuration of the liver in the individual case) equals the liver volume.

In a series of 304 cases (without autopsy confirmation) the relative volume as measured roentgenographically varied from 520 to 1,850 ml. Relative volumes of 550 to 860 ml. were considered normal; 800 to 900 ml. borderline; more than 900 ml. evidence of enlargement.

The author relates the determination of the liver volume to findings in cases of gallbladder and liver disease, diabetes, insulin-treated alcoholism, leukemia, polycythemia, cardiac insufficiency, chronic pyelonephritis, and chronic nephritis.

Six figures, including 4 roentgenograms; 1 table.

CAPT. JOHN C. RAMBAU, JR., M.C.
Lackland AFB, Texas

Methods of Cholecystography and Cholangiography. M. Bogatzki and R. Spieler. Fortschr. a. d. Geb. d. Röntgenstrahlen **94:** 30–43, January 1961. (In German) (Allgemeine Ortskrankenkasse Köln, Germany)

The methods of cholecystography and cholangiography as practiced in Teschendorf's Institute in Cologne, Germany, are discussed and illustrated. In the authors' experience the oral method has been perfected sufficiently to make intravenous cholecystography rarely necessary.

The contrast material (Telepaque, Biloptin, or Orabilex) is given in the evening following a fat-free meal. Filming is done the following morning with the stomach empty and usually without additional preparation, although a cleansing enema may prove necessary to eliminate disturbing intestinal shadows. For simultaneous visualization of the gallbladder and the bile ducts a second dose of tablets is given one to two hours prior to the examination. This method is recommended when a test meal is contraindicated. Instead of the usual fatty meal, consisting of egg yolk, 50 grams of milk chocolate is given. This is found equally effective and less objectionable. When the stomach has to remain empty, for a subsequent gastrointestinal examination, an injection of hypophysin or cholecystokinin may be substituted for the meal.

Emphasis is laid on the ability of the gallbladder to empty, and it is believed that a functional disturbance exists when the organ fails to contract. Various views in the prone, supine, and erect positions, as well as fluoroscopy with compression and spot-films, are often necessary to differentiate between small calculi and polyps. A comprehensive study may also result in good visualization of the bile ducts and thus an intravenous study can be avoided in most instances.

In routine examinations the gallbladder is visualized in 90 per cent of the cases. Occasionally, a double or triple dose may yield additional instances of satisfactory visualization. In the remainder of the cases, as well as in specific problems such as may arise after cholecystectomy, the intravenous method has to be considered. Care must be taken to avoid untoward reactions. Twenty cubic centimeters of Cholografin is injected very slowly over a period of fifteen minutes. In twenty to thirty minutes the bile ducts can be visualized, but the gallbladder as a rule fills only two hours later. The intravenous method is contraindicated in patients with myocardial damage and disturbances of intraventricular conduction.

Twenty-three roentgenograms.

ERNEST KRAFT, M.D.
Northport, N. Y.

Roentgenologic Observations in Cases of Fistulae of the Biliary Tract. William H. Shehadi. J.A.M.A. **174:** 2204–2208, Dec. 31, 1960. (1348 Midland Ave., Bronxville, N. Y.).

During the past ten years a total of 22 patients with a roentgen diagnosis of biliary tract fistula were seen at the New York Polyclinic Medical School and Hospital. Eighteen of the fistulas were internal: 9 spontaneous and 9 related to biliary tract surgery.

Roentgen findings in the 9 cases of spontaneous internal biliary fistula are reported. The presence of air in the biliary tract on the plain film of the abdomen is diagnostic of internal biliary fistula, with the rare exception of incompetence of the sphincter of Oddi. Actual delineation of the site of origin or point of communication between the biliary and gastrointestinal tracts cannot be obtained, however, without the use of contrast material.

Barium in the gastrointestinal tract will reflux into the biliary system through the fistula, fill the large radicals, and usually give excellent demonstration of the point of communication. In sphincteric incompetence, the normal anatomic landmarks are maintained and no abnormal communication can be established.

The author's attempts to visualize the biliary tree by oral cholangiography (by administration of such media as Telepaque) have been unsuccessful.

Following intravenous cholangiography, the visualization of the primary and secondary ducts depends on the nature and size of the fistula. If it is sufficiently small to create adequate back-pressure, visualization of the greater portion of the biliary tree will result. If the opening is wide, only the tertiary and, to a lesser extent, the secondary, but not the primary biliary radicals may be visualized. The tertiary or minute biliary radicals are the most frequently seen. Often there is some clubbing or dilatation, occasionally with intermingling of air, presenting a "frothy" pattern. This occurs in the upper portion of the liver, rarely in the dependent radicals. When the larger bile ducts are air-filled, it is hardly possible to detect the presence of Cholografin within them. With the absence of air, as may occur soon after the severance of common or hepatic bile ducts, Cholografin will outline the ducts up to the point of injury.

Six roentgenograms.

RICHARD H. GREENSPAN, M.D.
Yale University School of Medicine

THE MUSCULOSKELETAL SYSTEM

The Natural History of Hallux Valgus in Adolescence and Early Adult Life. Harry Piggott. J. Bone & Joint Surg. **42-B:** 749–760, November 1960. (37 Ennerdale Drive, London, N.W. 9, England)

A study was made of 113 patients (110 females; 3 males) with hallux valgus who were first seen during the growing period and had not at any time had surgical treatment. An attempt was made to trace the natural evolution of the deformity, with particular attention to any feature which in the early stages might serve as a guide to the structural prognosis of the individual foot. The youngest patient was seven years of age; the oldest attending for follow-up examination was thirty-six. The longest period of observation in an individual was twenty-one and a half years, with an average of five years and one month. The radiological material consisted of 216 feet with final standardized radiographs; 76 feet with one or more earlier standardized radiographs, 34 feet with nonstandardized radiographs. There were three distinct patterns in the relationship of the articular surfaces of the first metatarsophalangeal joint to each other as seen radiologically. In the first, these surfaces were completely congruous, as in the normal foot, their central points lying opposite each other. In the second the distal articular surface was deviated laterally on the proximal articular surface, leaving the medial end of the latter exposed. In the third the base of the proximal phalanx was subluxated laterally off the metatarsal head. As judged from the earliest available anteroposterior films, there were 20 feet in the congruous group, 81 in the deviated group, and 114 in the subluxated group.

The author concludes that pathological hallux valgus may be differentiated from an increase in a normal valgus alignment of the great toe by the relationship to each other of the articular surfaces of the first metatarsophalangeal joint; these are congruous in the normal joint but displaced on each other in the pathological. The earliest change is lateral deviation of the proximal phalanx on the metatarsal head, which may progress rapidly to subluxation, an early change in a high proportion of cases and frequently present when the patient is first seen in adolescence. Once subluxation has occurred, progression of the deformity is likely. Metatarsus primus varus and hallux valgus increase at an equal pace. There is not enough evidence to be certain which of these is the primary change, but such as there is suggests that lateral deviation of the great toe occurs first, and that increase in the intermetatarsal angle is secondary to this. It is also suggested that hallux valgus should be regarded primarily and fundamentally as a subluxation, or tendency to subluxation, of the first metatarsophalangeal joint.

Ten roentgenograms: 7 drawings.

THEODORE E. KEATS, M.D.
University of Missouri

Malignant Form of Albers-Schönberg Disease in Early Infancy. T. Cvibah. Fortschr. a. d. Geb. d. Röntgenstrahlen **94:** 76–81, January 1961. (In German) (Gebiets-Kinderkrankenhaus, Novi Sad, Yugoslavia)

Albers-Schönberg's osteopetrosis is an hereditary bone disease which usually starts in early infancy or in fetal life. In the benign form it is discovered incidentally when roentgen studies are done for other reasons. In the advanced stage, however, spontaneous fractures, severe anemia, and optic nerve atrophy occur. Other clinical findings are hypoplastic anemia, hepatosplenomegaly, and lymph-node hyperplasia. Intercurrent infections and massive hemorrhages due to thrombocytopenia are the usual causes of death.

The outstanding roentgenologic feature is a diffuse amorphous sclerosis of bones, the so-called marble bone, with complete obliteration of osseous texture. A lamellated pattern of dense transverse lines develops in the metaphyseal portion of long bones and at the iliac crest. The skull base becomes sclerotic, and vertebral bodies present triple layering with a central radiolucent zone and sclerotic upper and lower plates.

The case of an infant is reported in whom convulsions and fever developed soon after birth. A roentgenogram of the chest at three weeks of age showed eburnation of the ribs. A subsequent skeletal survey revealed amorphous sclerosis of all bones, with complete obliteration of osseous texture. The base of the skull was markedly sclerotic, and the vertebral bodies presented the typical triple layering. There was metaphyseal flaring of the tubular bones, with serrated end plates, but transverse striations developed only four months later, following intensive antirachitic treatment. These two changes were believed to be due to disturbed ossification in the varying stages of the disease rather than to associated rickets. The so-called embryonic stage in newly developed bone was also observed. This showed normal density occurring during a transient period in which the sclerotic process had ceased.

The patient was followed for ten months. During this time an aplastic anemia developed, with extramedullary hematopoiesis. There was enlargement of the liver, spleen, and lymph nodes. Characteristic changes were also found in blood smears and needle biopsies of the lymph nodes.

Six roentgenograms; 1 photograph.

ERNEST KRAFT, M.D.
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Suppurative Arthritis of Infancy. Some Observations upon Prognosis and Management. G. C. Lloyd-Roberts. J. Bone & Joint Surg. **42-B:** 706–720, November 1960. (Hospital for Sick Children, Great Ormond St., London, W.C. 1, England)

Occasionally infants with pyogenic arthritis exhibit alarming radiographic signs which may give a false impression of the extent to which the joint has geen damaged by the infection. The prognosis may in fact be relatively good and a favorable outcome predicted with confidence in some of these children. Reliance should not be placed on radiological evidence alone. The final shape of the articulating surfaces is dependent not upon the degree of decalcification of the ossific nucleus or the nearby metaphysis (these changes are reversible), but upon the damage caused to the epiphyseal cartilage and plate which cannot be seen in an early radiograph.

Thirteen cases are reported to illustrate certain features of infantile pyogenic arthritis affecting the knee and hip; all of the patients were seen within the last three years.

Attention is drawn to the powers of resistance of the growing ends of bones in suppurative pyogenic arthritis of the knee and hip in infancy. It is emphasized that a translucent zone in the radiograph does not necessarily mean that this part of the bone, epiphyseal

cartilage, or plate is destroyed. Diagnostic criteria are described to confirm that cartilage or decalcified bone has survived the infection in the knee joint.

Pyogenic arthritis of the hip presents greater difficulties in diagnosis and greater issues are at stake. It is recommended therefore that the hip joint be manipulated or explored if radiographic findings and physical signs suggest that destruction of the joint has either caused dislocation or has so damaged it that dislocation is likely to occur in the future. In favorable cases stability may be restored to the hip. In the others a diagnosis of irreparable destruction is established and the surgeon is satisfied that an opportunity to help the patient has not been lost.

Thirty-one roentgenograms; 5 photographs.

THEODORE E. KEATS, M.D.
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Noninfectious Arthritis in Small Bones and Joints: Roentgenologic Manifestations. Russell F. Scalf and Ji-Toong Ling. Arch. Int. Med. **107:** 23–30, January 1961. (University of Louisville School of Medicine, Louisville, Ky.)

The authors outline the most important roentgen manifestations of frequently encountered arthritic diseases affecting the hands and feet and summarize the differential diagnostic points between the more common types.

Osteoarthritis: The early roentgenologic changes of osteoarthritis in general are sharpening of the articular margins, spur formation, sclerosis of the articular margin, narrowing of joint space, pseudocyst formation. Later, there are increasing spur formation, marked cartilage destruction with sclerosis and flattening of articular margins, fringe osteophytes, and loose bodies.

Rheumatoid Arthritis: In rheumatoid arthritis, the early roentgen changes consist of periarticular soft-tissue thickening and edema, osteoporosis of bones near affected joints, erosion of articular margins, and some narrowing of the joint space due to cartilage destruction. Later extreme osteoporosis develops; progression of cartilage destruction results in obliteration of the joint space and bony ankylosis. Subluxation or dislocation may occur. Deformity of the part due to soft-tissue contraction and subluxation usually is the final result.

Gouty Arthritis: Initially, in *acute* gouty arthritis there are usually no radiographic signs except soft-tissue edema. Eventually, repeated acute attacks have incomplete remissions and leave radiographic changes in the joint. In *chronic* gouty arthritis, "punched out" areas appear at the articular margins of the affected bone. These are usually close to the joint and are few and scattered, which distinguishes them from the marginal erosions of rheumatoid arthritis. Large uncalcified deposits may erode the bone at the joint and involve the articular cartilage. Cartilage destruction produces narrowing of the joint space, sometimes progressing to bony ankylosis or complete disorganization of the joint. As the disease progresses, urate deposits in soft tissues and bones increase and larger "punched out" areas appear in the shafts of the bones. Later soft-tissue or bone deposits may become calcified, producing a so-called "gouty chalk-stone."

Psoriatic Arthritis: The early changes of psoriatic arthritis are almost impossible to distinguish from those of rheumatoid arthritis except for the associated skin or nail lesions. The only important radiographic differential signs are a lack of appreciable demineralization in the early psoriatic type and a predilection for involvement of the terminal interphalangeal joints. Later the tufts of the affected distal phalanx (particularly of the great toe) become demineralized or destroyed, producing a "pencil point" appearance, and destruction, mutilation, and atrophy of the osseous structures about the joints become increasingly severe, so that often the radiographic end-result appears to be an actual widening of the joint space.

Sarcoidosis: The osseous changes of sarcoidosis are usually a painless, fusiform, soft-tissue swelling of the affected fingers and toes. Large pseudocysts form close to the articular surface, usually near the center of the shaft, and there is absorption of trabeculae and of the cortex of the phalanges. The combination of the formation of pseudocysts and their coalescence, plus trabecular destruction and cortical absorption, may eventually completely dissolve a portion of a phalanx, giving an appearance that is almost pathognomonic.

A table of important differential points is presented. Nine roentgenograms.

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Tumoural Gummatous Yaws. W. P. Cockshott and A. G. M. Davies. J. Bone & Joint Surg. **42-B:** 785–787, November 1960. (University College, Ibadan, Nigeria)

The authors present 2 examples of tumoral gummatous yaws, one from Nigeria and one from Uganda. The first patient, a twenty-seven-year-old Negro, had a two-year history of painless swelling of the lower forearm. A radiograph showed an unusual productive and destructive lesion involving the distal third of the radius and ulna. On the medial side of the ulna was considerable organized fusiform accretion of periosteal new bone. A similar process was present at the proximal end of the radial lesion. A fairly abrupt transition occurred between this zone and an area where there was no remnant of the original bony structure. The normal bony tissue had been replaced by a soft-tissue mass which contained many lace-like fragments of bone, giving rise to a bizarre mottled appearance. Brachial arteriography showed the lesion to be displacing normal vessels by reason of its mass, but there were no new vessels in the area.

The second patient was a twenty-five-year-old Negro who complained of weakness of the hand and swelling of the left forearm. He gave a history of a generalized yaws eruption in childhood and also vague bone pain two years previously. A fusiform swelling of the forearm was hard and tender on pressure. Radiography disclosed marked fusiform expansion of the distal two-thirds of the radius and to a lesser extent of the ulna. This was due to exuberant periosteal new bone formation combined with the lack of structure of the medulla. The same type of mottled appearance was seen as in the first case.

Several examples of this type of process are said to have been seen in the past two years in Ibadan (Nigeria), all in young men with positive serological tests and no obtainable history of syphilis. The dominant lesion has always been in the upper limbs, with a predilection for the end of a bone. The radiographic response to penicillin has been negligible.

The distinction between yaws, syphilis, and endemic syphilis is not possible radiologically, and even with refinement in serological investigation, such as the

treponemal immobilization test, no absolute classifying criteria are available.

Three roentgenograms; 1 photomicrograph.

THEODORE E. KEATS, M.D.
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Multiple, Slowly Growing Osteogenic Osteoblastic Tumor. M. Smokvina, K. Ribkin, A. Bunarević, P. Franulović, and A. Zimolo. Fortschr. a. d. Geb. d. Röntgenstrahlen **94:** 44–56, January 1961. (In German) (Universität in Zagreb und Militärkrankenhaus, Zagreb, Yugoslavia)

A case of a slowly progressive osteoblastic tumor, observed over a period of six years, is reported. The patient was a housewife, aged twenty-six when first seen because of sharp pain in her left elbow. Roentgenograms revealed marked hyperostosis of a flowing type in the distal third of the left humerus. A skeletal survey disclosed dense islands of bone in the pelvis, both hips, right humerus, dorsolumbar vertebrae, and cranial vault. All laboratory tests were negative except for slight increase of alkaline phosphatase. Biopsy studies revealed only compact bone and numerous nests of osteoblasts. No other member of the family was similarly afflicted.

In the course of six years the hyperostosis progressed markedly in some areas and more slowly in others. Regular bone tumors developed at the left temporal bone and pelvic girdle. In the femora an endosteal flow extended distally to the supracondylar areas and completely obliterated the medullary canal proximally.

Gradually neurologic manifestations developed, with paresis of the lower extremities, caused by intraspinal pressure of the bone tumors on the spinal cord. Anemia and increase of the sedimentation rate were only slight, but there was a rise in alkaline phosphatase up to 76 Bodansky units, which denoted marked osteoblastic activity.

Myelography revealed a block at the C6 level and, twenty-four hours later, at the D7 level, which necessitated laminectomies for decompression. The downhill course continued as incontinence, anemia, leukocytosis, and increase in sedimentation rate developed. The left fourth rib was resected for diagnostic purposes. Pleural and pericardial empyema followed. Finally septicemia ensued, causing the patient's death.

At autopsy all visceral organs were found to be free of metastatic lesions. Histologic studies of the bony masses revealed sharply demarcated compact bone tissue with interspersed osteoblasts arranged in clusters, strands, and palisades. There was no evidence of osteogenic sarcoma. While the disease was accidentally found at the age of twenty-six, six years prior to death, it is believed that its development actually had begun a long time before its discovery.

Twenty-two roentgenograms; 5 photomicrographs; 1 drawing.

ERNEST KRAFT, M.D.
Northport, N. Y.

Angiography of Aneurysmal Bone Cyst. Å. Lindbom, G. Söderberg, H. J. Spjut, and O. Sunnqvist. Acta radiol. **55:** 12–16, January 1961. (Karolinska Sjukhuset, Stockholm, Sweden)

The characteristic roentgen appearance of aneurysmal bone cysts is a ballooned-out distention of the periosteum, usually outlined by a paper-thin subperiosteal shell of bone under which an eccentric destruction of both the cortex and the cancellous bone is evident. Histologically these tumors contain large, distended or distorted, thin-walled blood spaces.

The authors obtained angiograms of 3 aneurysmal bone cysts which showed uniform appearances and some characteristic features. The distal part of the femoral shaft of a 28-year-old man was involved in the first case; in the second, the proximal metaphysis of a tibia of a 13-year-old girl was the site of the lesion; in the third, the proximal metaphysis of an ulna of a 16-year-old girl was affected. The examinations were all performed with a serial technic, and in 2 of them an automatic changer was used. The arteries leading to the cysts were dilated, markedly in 2 cases and slightly in the other. During the passage of the contrast medium a slight but definite degree of opacity was noted throughout the whole area of the cyst, having a certain patchy distribution which persisted late in the venous phase. There was no peripheral hypervascularized zone as in malignant tumors. The veins leading from the lesion were filled somewhat earlier than the others, indicating an arteriovenous shunt, which, however, was considerably less than that in most malignant tumors. The increased opacity must be due to the presence of contrast material in the vascular lumina of the cyst. Whether the medium passes through the many small vessels of the fibrous stroma or the large vascular lumina, or through both, cannot be gathered from angiography. The authors feel, however, that the patchy opacities could be explained by the presence of diluted contrast medium in the large vascular spaces.

In some cases where the roentgen appearance of an aneurysmal bone cyst is atypical, and the thin, blown-out shell of bone is absent, angiograms are particularly helpful in differentiation from a malignant tumor. In the rare instance when the cyst is in or adjacent to an epiphyseal region the differentiation from giant-cell tumor on the ordinary roentgenogram is difficult, and angiography cannot be relied upon for distinguishing between the two conditions.

Nine roentgenograms; 2 photomicrographs.

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Renal Osteonephropathy. Sten Cronqvist. Acta radiol. **55:** 17–31, January 1961. (University Hospital of Lund, Sweden)

Renal osteonephropathy is a term used to describe skeletal changes sometimes seen in association with renal disease, both chronic renal insufficiency and selective tubular diseases. Roentgen changes of two types can be distinguished: those resembling rickets and those similar to osteitis fibrosa cystica generalisata. The former are seen before, the latter mainly after the closure of the epiphyseal line. Occasionally both types may be found in the same patient. Before epiphyseal closure, typical rachitic changes are seen in the distal long bones, particularly the radius and ulna. In more advanced cases there are general rarefaction, obliteration of all compact tissue, and coarsening of the trabeculae in the cancellous bone. These changes may also occur in the skull, with granular rarefaction and splitting of the lamina interna and lamina externa, sometimes with thickening of the bone. Deformation of the lower limbs may also be seen, due either to "softness" of the skeleton or to epiphyseolysis, at times resulting in dwarfism.

Radiographic findings in adults include granular or

generalized decalcification with or without derangement of trabeculae; osteoporosis; subperiosteal erosion, most frequent in the middle phalanges of the fingers; resorption of the lamina dura; metastatic and vascular calcification; osteosclerosis, especially in single or multiple vertebrae.

Seven cases are reported in this article. In some the vertebral changes were noted on routine chest and abdominal roentgenography. In 2 cases the spinal changes were initially slight with generalized rarefaction and irregular coarse trabeculation. Joint pain and/or stiffness were reported by most patients, and led to the roentgen examination of 4.

The mechanism of skeletal changes and calcifications is incompletely understood. Regression of rachitic changes in a 17-year-old boy in this series, after protracted treatment of acidosis, suggests that condition as the main cause of the bone abnormalities.

Primary hyperparathyroidism can produce radiographic changes of the same nature as those of renal osteonephropathy. The differential diagnosis in advanced cases with secondary renal insufficiency may be difficult and depends on a careful clinical history and biochemical studies. Other diseases to be differentiated are osteoporosis, Paget's disease, and hypervitaminosis D. In the final diagnosis, knowledge of the primary nature of the renal disease or of the malformation of the kidney is important. Low serum calcium and raised serum phosphate are suggestive. None of the roentgen changes of renal osteonephropathy are pathognomonic but, like the metastatic calcification in cases of chronic renal insufficiency, osseous changes, particularly of the rachitic type, should guide the examiner's thoughts to renal osteonephropathy.

Seventeen roentgenograms.

CAPT. ROBERT E. WILDIN, M.C.
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Symmetrical Bone Changes in Both Distal Extremities with Simultaneous Myositis Fibroblastica. K. Reinhardt. Radiol. clin. **30:** 52–63, January 1961. (In German) (Hüttenkrankenhaus Völklingen/Saar)

A 60-year-old patient showed changes of bone structure in the tibia, fibula, and the tarsal bones on both sides, with bony ankylosis of the ankle and tarsal joints, arthrosis of the knee joints, periostitis ossificans, myositis chronica fibroblastica, defects of the elastic layers of the arteries, thickening of the inner layer of the arteries and veins, swelling of the soft tissues, trophic ulcerations, necroses, severe pains, and disturbance of the blood circulation. The disease developed and progressed slowly for twenty-three years, finally necessitating amputation of the left leg. Later, the right leg was also affected. The etiology was not explained. Since no symptom complex of this nature could be found in the literature, it is possible that this was a specific syndrome.

Nine roentgenograms.

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Is Radiological Examination of the Twisted Ankle Necessary? J. S. Garfield. Lancet **2:** 1167–1169, Nov. 26, 1960. (St. Mary's Hospital, London, W.2, England)

A study was made of 111 patients with twisting injuries of the ankle to assess the value of radiology in determining the treatment and to define the indications for such examination. It was found that the clinical features alone give an unequivocal guide to diagnosis in three groups of cases, making radiological examination unnecessary. Forty-one of the 111 cases were in these groups.

Group I: Absence of swelling is a firm indication of the absence of any significant bony or ligamentous damage, whatever the circumstances of injury.

Group II: Tenderness localized to the base of the fifth metatarsal is a sure indication of fracture in this site only.

Group III: The absence of moderate tenderness, bruising, or swelling in a patient under sixty-one, who injures the ankle while walking, is a good indication that there is no major bony injury.

In the remaining cases, clinical features give only an inaccurate guide to the nature of the injury, and in these radiological examination is required. Even in the groups in which roentgen examination is actually unnecessary as far as treatment is concerned, it may be of medicolegal interest.

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Forced Inversion of Ankles. D. H. Nelson. J. Bone & Joint Surg. **42-B:** 793, November 1960. (Royal Victoria Hospital, Folkestone, Kent, England)

The author emphasizes the importance of the forced inversion view for the complete evaluation of injury to the ankle. It is his practice to take this view in all patients referred with a history of injury to the ankle when the anteroposterior and lateral radiographs do not show a fracture. With the method of self-forced inversion employed, it is unlikely that further injury can be inflicted. Ligamentous damage may be demonstrated and occasionally a fracture not seen on routine radiographs may be detected.

Three roentgenograms; 1 photograph.

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GYNECOLOGY AND OBSTETRICS

Effect of a Radiation Opaque, Water-Soluble Medium on the Histopathology of the Endometrium. G. E. Seegar Jones and J. Donald Woodruff. Am. J. Obst. & Gynec. **80:** 337–340, August 1960. (Johns Hopkins Hospital, Baltimore, Md.)

During the past eight years the authors have occasionally performed a curettage at the time of hysterosalpingography or shortly thereafter on patients investigated for infertility or repeated miscarriages. The purpose of the study reported in this paper was to determine (1) if this practice might be in any way harmful to the patient and (2) if the interpretation of the endometrial findings is histologically valid.

During the years 1950 to 1955, some 335 patients were subjected to hysterosalpingography with the use of a water-soluble medium and curettings of 120 of these were available for examination. Curettage was done prior to roentgenography in 47 patients who served as controls; immediately following the hysterosalpingography in 23; within the month in 28; later than the following month in 22. Specimens were examined without knowledge of the relationship of the roentgen procedure to the curettage and the endometrium was evaluated according to the cycle and with special reference to any inflammatory change or other tissue reaction.

Tubal occlusion from pelvic inflammatory disease was shown in 23 of some 50 hysterosalpingographic studies performed for infertility. In the whole group, it was thought that perhaps 3 pregnancies were attributable to the examination. One of these 3 terminated in an ectopic pregnancy. There was no evidence, either clinically or pathologically, of a tendency for exacerbation of old pelvic inflammatory disease following the procedure, and in only 3 patients were there mild clinical symptoms of a nonspecific reaction, characterized in 1 case by abdominal pain and in 2 by a low-grade fever of two days duration.

In 20 examinations made to determine the cause of repeated miscarriages, an unexpectedly high number of uterine anomalies were found: 9 congenitally defective uteri and 3 submucous fibroids.

One examination was made to confirm the diagnosis of traumatic amenorrhea.

Histologic findings were indistinguishable in those patients with hysterosalpingography prior to the curettage from those where the roentgen examination followed the curettage. It would seem (1) that the use of a radiation-opaque, water-soluble medium is seldom associated with endometrial reactions; (2) that it is safe to proceed with immediate curettage; (3) that the interpretation of the histologic findings, following the procedure, is valid.

Use of Femoral Arteriography in Assessment of Bleeding in Pregnancy. Richard L. Bernstine, James H. Nelson, Jr., Nicholas A. Garcia, III, J. Wilson Huston, and Charles Gartenlaub. Am. J. Obst. & Gynec. **80:** 1161–1167, December 1960. (U. S. Naval Hospital, St. Albans, N. Y.)

An arteriographic study was made of 21 consecutive pregnant women (over a six-month period) with unexplained vaginal bleeding. The weeks of gestation at the time of the test varied from four to forty. Thirty cubic centimeters of 50 per cent Hypaque was injected as rapidly as possible into the femoral artery and roentgenograms were obtained three and fifteen seconds after completion of the injection. If the placenta was seen to be low-lying on the anteroposterior projection, a second injection was made and a lateral film obtained at three seconds. The lateral projection gives more precise localization.

In all the cases of this series, it was possible to demonstrate the position and extent of the placenta accurately by arteriography, and the presence of abruptio placentae was also determined.

During the course of the study a previous isolated observation was confirmed, namely, pooling of contrast material in extravascular spaces. Placental examination at the time of delivery established correlation of this finding with the histology of the placenta. In 2 cases sufficient time elapsed to allow organization of the infarcted area. In the other cases the interval between examination and delivery was shorter and the placentas exhibited recent adherent clots. In 1 case the radiologic findings could not be distinguished from those of premature separation of the placenta. In 3 cases in which the gross appearance revealed an adherent marginal clot which could be interpreted as evidence of "marginal sinus rupture" or abruptio placentae, the radiologic findings did not show pooling of the medium. However, persistence of the contrast agent was observed within the placental sinusoids on the fifteen-second film. Further investigation may indicate that this is evidence of impeded placental circulation.

There were no complications in the 21 cases reported.

Seven roentgenograms; 1 extensive table.

THE GENITOURINARY SYSTEM

Roentgen Localization in Percutaneous Puncture Biopsy of the Kidneys. E. Krokowski and A.-A. Kollwitz. Fortschr. a. d. Geb. d. Röntgenstrahlen **93:** 613–616, November 1960. (In German) (Frei Universität Berlin am Städt. Krankenhaus Westend, Germany)

In needle biopsy of the kidney, exact localization is important. Methods for localization include, beside direct operative biopsy, injection of contrast material under fluoroscopic control; retropneumoperitoneum; planigraphy (sometimes with lead markers). The authors' method is based on geometrical relationships. In the region of the kidney of the supine patient, a punctate lead marker is placed. The central roentgen ray is then directed to the proposed site of the biopsy and a film is made. The film-target distance is easily measured with the aid of the lead marker. This method has increased successful localizations from 72 to 95 per cent.

In making the puncture, the physiological motility of the kidneys has to be considered, and filming and biopsy should be done in deep inspiration and in the supine position. A foam-rubber pillow should be placed under the side of the biopsy.

Two roentgenograms; 1 diagram; 1 table.

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Cystic Calcification in the Kidney: Its Occurrence in Malignant Renal Tumors. Abram H. Cannon, Bert Zanon, Jr., and Bill G. Karras. Am. J. Roentgenol. **84:** 837–848, November 1960. (Wesley Memorial Hospital, Chicago, Ill.)

It has often been stated that simple cysts of the kidney may calcify, and calcification, nearly identical to that seen in simple cysts, has been recorded in renal hydatid cysts. The authors report 6 cases of cystic calcification, 5 within a clear-cell carcinoma (renal, 4 cases; retroperitoneal, 1 case) and 1 in a cortical adenoma. A valuable finding was that the distortion of the calyceal system in the malignant tumors seemed to be caused by a mass larger than the calcified cyst.

A complete evaluation of the etiology of all cystic calcifications is strongly recommended, as, regardless of the clinical symptoms, they may occur in either a malignant or benign tumor. Differentiation cannot be made except by surgical exploration.

Thirteen roentgenograms; 1 photograph.

ROBERT H. LEAMING, M.D.
Memorial Center, New York

Periarteritis Nodosa Complicated by Spontaneous Perinephric Hematoma. Roentgenographic Findings in Three Cases and a Review of the Literature. Bernard J. Ostrum and Parry D. Soder. Am. J. Roentgenol. **84:** 849–860, November 1960. (P. D. S., Philadelphia General Hospital, Philadelphia 4, Penna.)

Three cases of spontaneous perinephric hematoma secondary to periarteritis nodosa have been seen at

the Philadelphia General Hospital in the past two years. An extensive review of the literature reveals that this is a fairly uncommon complication of periarteritis nodosa as only 27 similar cases have been recorded. The first of the authors' cases was diagnosed only postmortem. The striking clinical and roentgenographic similarity of the subsequent cases led to their preoperative recognition.

The authors point out that this entity has a definite clinical and roentgenographic pattern. All 3 of the patients were hypertensive young males with symptoms of severe left lumbar pain and fullness. Excretory urograms all revealed a left-sided mass and nonvisualization of the left kidney. Retrograde pyelograms showed deviation of the ureter, extrinsic pressure upon the calyces, and only minor calyceal changes. The pathologic finding in each instance was perinephric hematoma, secondary to rupture of small aneurysms of the interlobar arteries.

Roentgen studies were performed in 12 of the collected series of 30 cases. A summary of these cases brought out that the combination of a large renal or retroperitoneal mass demonstrated on an abdominal roentgenogram, ipsilateral nonvisualization on excretory urograms, and an essentially normal retrograde pyelogram should lead the radiologist to suspect a vascular insult to the kidney with subsequent perinephric hematoma. Periarteritis nodosa, ruptured renal artery aneurysm, arterial renal infarction, renal vein thrombosis, and ruptured and/or dissecting aortic aneurysm are conditions that should be included in the differential diagnosis. This triad of roentgen findings along with a clinical picture of hypertension, arthralgia, myalgia, gastrointestinal complaints, low-grade fever, and weight loss in a male in his twenties or thirties should, however, strongly suggest the diagnosis of periarteritis nodosa complicated by spontaneous perirenal hematoma.

Aortography may enhance the demonstration of the numerous small intrarenal aneurysms of periarteritis nodosa. In the one of the authors' cases in which this study was performed, aneurysmal dilatation could be recognized in retrospect.

Ten roentgenograms; 2 photographs; 2 tables.

ROBERT H. LEAMING, M.D.
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The Value of Dehydration in Intravenous Pyelography—An Experimental Study. J. Scott Dunbar, Douglas W. MacEwan, and Francois Hebert. Am. J. Roentgenol. **84:** 813–836, November 1960. (Montreal Children's Hospital, Montreal, Que., Canada)

The authors review the literature on the value of dehydration in intravenous pyelography back to 1929, when Uroselectan was first used, and report the results of a "blind study with cross-over" on 21 healthy adult male volunteers. Each of the subjects was examined twice, once without any preparation and once when prepared only by fasting for about fifteen hours. The interval between the two examinations was two weeks.

The ages of the volunteers ranged from twenty-one to forty-seven, with an average of twenty-eight years. No one was included in the study who gave a positive history of allergy, drug sensitivity, or urinary tract disease. Twenty-five cubic centimeters of 60 per cent Renografin was injected through an antecubital vein. Films were exposed at five, ten, fifteen, thirty, and sixty minutes. The subject voided after the thirty- and sixty-minute exposures and records were made as soon as possible of the volume, specific gravity, and *p*H of all the voided specimens, which were then preserved for densitometry, iodine concentration, and osmolarity estimations. Following the thirty-minute roentgenogram, 40 oz. of water was drunk as rapidly as possible. This "water load" did not in any case appear to contribute toward the diagnostic quality of the pyelogram.

No significant allergic or other reactions were encountered.

By exclusion, the most important variable in the study of these normal volunteers was the individual difference: the pyelograms of one person with or without dehydration were consistently better than those of another. This difference between individuals was more significant than the difference in evaluation between two observers or between two observations by the same reader.

The results were evaluated twice by two different observers who had no knowledge of the identity or state of preparation of the volunteer, and an attempt was made to correlate the roentgenographic findings with chemical analyses of urine and *in vitro* urine density estimations and measurements. There was a slight and consistent improvement in quality of the intravenous pyelogram following dehydration. The improvement is minimal in the early stages (five to fifteen minutes) of the examination and becomes greater in the latter half of the first hour.

These findings would suggest that the adult patient should be subjected to a period of dehydration prior to intravenous pyelography, if this does not cause undue inconvenience, discomfort, danger, or delay. If for any reason it is necessary to carry out the examination without preparation by dehydration, pyelograms of comparable quality can be obtained by taking a larger number of films early in the examination.

Experiments of the same nature were carried out in rabbits with strikingly similar results.

Twenty roentgenograms; 1 photograph; 2 charts; 3 tables.

ROBERT H. LEAMING, M.D.
Memorial Center, New York

Vaso-Seminal Vesiculography in Hypertrophy and Carcinoma of the Prostate with Special Reference to the Ejaculatory Ducts. Gunnar Willer Vestby. Acta radiol. Supplement 199, 1960. (Ullevål Hospital, Oslo, Norway)

The author discusses the value of vaso-seminal vesiculography and reports his experience in 181 patients with benign hypertrophy and 49 patients with carcinoma of the prostate. The lower portions of the spermatic tract in 45 prostatic specimens were also contrast-filled and examined roentgenologically. The observations are correlated with the pathological findings and other methods of diagnosis.

Vaso-seminal vesiculography is done in conjunction with vasectomy. At Ullevål Hospital, from which this report comes, this latter procedure is routine for most cases of urinary tract difficulty due to prostatic hypertrophy or carcinoma so as to prevent epididymitis. An incision is made through the scrotum, under local anaesthesia. After transection of each ductus deferens, the distal end is cannulated.

Exposure is made during injection of contrast medium, 1.5 to 2.0 c.c. of 45 per cent Hypaque for each exposure. Injection is painless. Four views are obtained: a craniofrontal view with tube angulated 15° toward the feet, a frontal view, and both obliques.

The appearance of the ejaculatory ducts is considered the most valuable feature in the differentiation between carcinoma of the prostate and benign hypertrophy. Since prostatic carcinoma in most cases originates posteriorly or posterolaterally, there is usually early involvement of the ejaculatory ducts. The characteristic findings are a narrowed lumen, with rigid irregular contours, absence of circular folds, and inability to dilate. These findings do not occur in other conditions. In the more advanced lesions the seminal vesicles may also be involved. In benign hypertrophy the findings are practically the opposite of those in carcinoma. In inflammatory disease some narrowing can occur, but the involvement of the seminal vesicles is often greater and the terminal portion of the excretory duct is spared. In carcinoma, on the other hand, the involvement starts medially. Malignant tumors located anteriorly or anterolaterally cannot be located by this technic. These, however, represent a relatively small group.

In benign hypertrophy the luminal contours of the ejaculatory ducts are smooth but regular. The normal circular folds are preserved. Frequently the ducts are dilated throughout their extent. In 59 per cent of the author's benign cases the ducts were wider than 3 mm. at the junction of the middle and lateral thirds. The average normal diameter is 1.5 mm. There is a greater resistance to the injected fluid at the orifice on the verumontanum. This may account for the dilatation of the ducts.

Changes considered typical were seen in 93.4 per cent of patients with benign hypertrophy. In 6.6 per cent carcinoma could not be excluded. In the patients with prostatic carcinoma changes typical of this disease were present in 69.4 per cent. There were no false positives. In 18.4 per cent the findings were strongly suggestive of carcinoma but not pathognomonic; in the remaining 12.2 per cent they were negative.

The author states the following indications for vasoseminal vesiculography: "1. In all cases of benign hypertrophy and prostatic carcinoma in which the diagnosis is still uncertain after routine examination. 2. In all cases of prostatic carcinoma in which radical prostatectomy is contemplated and it is desirable to know the extent of the lesion. 3. In all prostatics when vasectomy is proposed."

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TECHNIC

Medical Progress: Kineradiography. Majic S. Potsaid. New England J. Med. **264:** 178–185, Jan. 26, 1961; 232–237, Feb. 2, 1961. (Harvard Medical School, Boston, Mass.)

The author presents a rather comprehensive discussion of cinefluorography and suggests that cineradiography, or perhaps "kineradiography," be used as an inclusive term for studies of motion obtained by radiologic means regardless of the augmenting system (for example, electron image intensifier, solid-state image intensifier, television, magnetic tapes, and films of a kinescope). Motion-picture studies are almost as old as x-rays themselves (MacIntyre: Arch. Skiagraphy **1:** 37, 1897), but with the perfection of brighter fluoroscopic images through intensification and amplification, a practical approach to the recording of motion has been made possible. A satisfyingly detailed yet palatable discussion of the design, physics, and optic physiology behind kineradiography is presented. It is the appreciation of the physiology and pathophysiology of body structures that gives kineradiography its medical importance.

The second part of this paper discusses the advantages of kineradiography with respect to radiation dose, earlier diagnosis, teaching, communication of information, and possible future developments.

No new theories or methods are presented, but the ample bibliography (84 references) and broad discussion make this contribution an excellent reference for those contemplating the use of kineradiography or for those who are merely interested in the subject.

Eleven figures, including 6 roentgenograms; 2 tables.

H. N. STURTEVANT, M.D.
Springfield, Mo.

A Scintillation Counter Technique for the X-Ray Determination of Bone Mineral Content. Edward H. Mayer, Hebert G. Trostle, Eugene Ackerman, Harald Schraer, and O. Dayle Sittler. Radiation Res. **13:** 156–167, July 1960. (E. H. M., Bell Telephone Laboratories, Murray Hill, N. J.)

The authors describe a preliminary model of a scintillation counter apparatus for the determination of the mineral content of bone. The accuracy of bone density measurements obtained with the scintillation counter technic is as good as that attainable with the older x-ray film method. Since it eliminates the film as a source of error and can reduce scattering error by means of a collimated beam, the scintillation counter technic may possibly be made the more accurate. X-ray film, on the other hand, has the advantage of providing a more permanent record of the bone and clearly shows the points on the bone where the trace path is located.

The scintillation counter was also used for a study of the errors resulting from x-ray scattering in the film technic, with the following results: (1) Scattering error in the x-ray film technic probably does not exceed 5 per cent for most bones. (2) Scattering error increases with the size of the bone. (3) Soft tissue surrounding the bone contributes a major portion of scattered radiation. (4) Shorter wavelengths are scattered more than longer wavelengths. (5) The wedge is a good analog of bone but not of soft tissue.

It should be noted that the bone density coefficients obtainable from successive measurements on the same film may vary by about 5 per cent, with the present film technic. Thus, the error due to scattering can probably be neglected in comparison to other errors in the bone density determination by x-ray films.

Eight figures.

RADIOTHERAPY

Is Primary Surgical Treatment of Malignant Melanoma Still Recommended Today? H. Kapp-Schwoerer. Schweiz. med. Wchnschr. **90:** 1494–1497, Dec. 28, 1960. (In German) (Radiotherapeutische Zentralinstitut des Kantonspitals St. Gallen, Switzerland)

The problems of early diagnosis and therapy of malignant melanoma are reviewed, and it is pointed out that the good results of primary x-irradiation are often overlooked, especially in surgical textbooks. A report is made on 30 cases of melanoma of clinical Stage I (histologically determined) which were sent to the author's institution for postoperative irradiation. In the short period of observation, 1954 to 1960, 12 of the patients died with metastases and 8 more showed certain metastases. In the same period, 11 cases which were treated primarily by irradiation showed no metastases up to the time of this report. The short follow-up may make the results seem overfavorable for primary x-irradiation in these cases, but, on the other hand, a less favorable result is to be expected after a longer time in those cases in which the primary treatment is surgical.

At the Kantonspital St. Gallen, from which this report comes, primary x-irradiation of melanoma is recommended, with later electro-excision and, if the melanoma is situated in an extremity, prophylactic postirradiation of the regional lymph nodes. The author urgently advises against primary surgery for this tumor.

Management of Angiomas. Dan J. Kindel. J. A.M.A. **174:** 872–877, Oct. 15, 1960. (809 Union Central Bldg., Cincinnati 2, Ohio)

On the basis of experience with all types of dermatologic lesions including more than 600 angiomas, the author is confident that soft and ultrasoft x-ray therapy is effective in many cases of superficial strawberry and hyperplastic angiomas. The cosmetic results are excellent and there is no danger of serious sequelae.

The port-wine stain and mature cavernous angioma often coexist, they rarely disappear spontaneously, and only partial regression may be expected following radiation therapy. For immature angiomas or strawberry nevus (the most common of the three types) radiation therapy is strongly advised and is the simplest, least painful, and most effective approach. These lesions are sensitive to radiation at the time of their appearance but tend to lose much of this character within twelve to eighteen months. A tendency toward spontaneous involution is present, with a better prognosis, in those lesions which enlarge during the first few months of life, but the prediction of the course of any given lesion without treatment is impossible. Many persist, and complications may occur. Prompt treatment with low energy x-radiation is urged and "watchful waiting" for spontaneous involution is discouraged.

Details of dosage are given.

Twelve photographs; 1 table.

WILLIAM MARTEL, M.D.
University Hospital, Ann Arbor, Mich.

Cancer of the Oral Cavity Treated at the Norwegian Radium Hospital. Torleif Alsos. Cancer **13:** 925–931, September-October 1960. (Norwegian Radium Hospital, Oslo, Norway)

Cancer of the oral cavity is rare in Norway, accounting for only about 1 per cent of all cancer mortality. An average of 75 cases are encountered each year, of which 70 per cent (about 50 patients) are treated at the Norwegian Radium Hospital. During the period 1932–1957, a total of 1,289 patients were treated at the above institution, 1,219 primarily and 70 for recurrence after primary therapy elsewhere. The frequency of cancer of the oral cavity is much higher in men than women, 65 and 35 per cent respectively in the present series. The frequency is much higher in urban than in rural districts.

A total of 648 patients had primary tumors located in the gingiva, the floor of the mouth, the bucca, or the hard palate. In about a fourth of these (150), roentgenograms obtained on admission revealed bone destruction; in 40 (6 per cent) destruction was demonstrated later. It was most frequent in patients with carious teeth and patients with metastases.

In the period covered by this report, treatment of cancer of the oral cavity at the Norwegian Radium Hospital was a combination of surgery and radiotherapy. When the tumors were small and well defined, electrocoagulation was often performed, with radium intubation before or afterward. The majority of the tumors, however, were treated with telegamma irradiation from a radium apparatus. Ordinarily x-ray therapy was used for the more extensive lesions with lymph-node involvement. Since 1958, the teleradium apparatus has been replaced by a radioactive cesium source. Previously, if the metastases did not respond satisfactorily to radiotherapy after a period of six to eight weeks, a radical neck dissection was performed. In recent years, a radical neck dissection is carried out as soon as the primary tumor has been brought under control. Prophylactic lymph-node dissection is usually not done. Radical extraction of teeth is considered advisable before irradiation.

The crude survival rates in this series were 28 per cent and 20 per cent after five and ten years respectively, with the corrected survival rates 37 per cent and 35 per cent. Women had a higher five-year survival rate than men, because of a lower incidence of metastasis both on admission and later.

Four graphs; 8 tables. H. N. STURTEVANT, M.D.
Springfield, Mo.

The Diagnostic and Prognostic Value of Oral Smears in the Radiotherapy of Carcinoma of the Oral Cavity and Oropharynx. William Umiker, Isadore Lampe, and Robert Rapp. Am. J. Roentgenol. **85:** 69–77, January 1961. (University of Michigan Medical Center, Ann Arbor, Mich.)

The authors have previously described interim results in studying the radiosensitivity of benign and malignant cells in oral carcinoma (Cancer **12:** 614, 1959. Abst. in Radiology **74:** 698, 1960). The present report is their final evaluation of certain histologic and histochemical changes in irradiated cells as indices of the effect of roentgen therapy.

Direct smears were obtained from the surfaces of 55 oral carcinomas prior to, during, and after irradiation. In benign squamous cells radiation changes

(cellular and nuclear enlargement, cytoplasmic vacuolization, multinucleation) were usually distinct after five to seven days of treatment, but the radiation response had no practical value in prognosis of the clinical results. In malignant cells quantitation of these changes proved difficult and was abandoned. Maturation, as determined by the nucleocytoplasmic and the cornification indices, was striking in only a few cases and showed no statistically valid correlation with clinical observations.

A good correlation was observed between the nucleoprotein patterns of the malignant cells and the results of irradiation; thus, an increased number of Caspersson type B cells (rich in nucleolar ribonucleic acid and relatively poor in nuclear desoxyribonucleic acid) was a favorable prognostic sign. Marked variations in cellular exfoliation of otherwise similar tumors could not be satisfactorily explained. Substantiation of the initially reported increased propensity for abundantly exfoliating tumors to metastasize was only partial.

The presence of malignant cells in oral smears taken at the end of treatment does not preclude irradiation arrest, and many patients showed conversion of positive to negative smears following completion of treatment. Oral smears taken during the first three months after completion of therapy are of practical prognostic value. Each of the 13 patients who had positive smears during the postirradiation phase either had residual or recurrent neoplasm and 6 had died at the time of this report; only 3 (11 per cent) of the 28 whose smears were negative during this phase had residual tumor; in only 4 of these 28 did neoplasm subsequently develop, and all but 1 were alive at the time of this report.

Three figures; 2 tables.

PHILIP M. JOHNSON, M.D.
Montclair, N. J.

Preoperative Radiation in Treatment of Breast Carcinoma. Galen M. Tice. J.A.M.A. **174:** 1403–1407, Nov. 12, 1960. (University of Kansas School of Medicine, Kansas City, Kans.)

Forty patients with breast carcinoma, first diagnosed between 1936 and 1942, received roentgen irradiation (250 kv) *before* surgery. The diagnosis was confirmed by biopsy in all but 4 advanced cases, and the follow-up was excellent in almost all instances. A 55 per cent five-year survival was noted, and 7 patients were alive twenty years after the diagnosis was established. The survival findings are shown in the accompanying table, which also gives the stage of the tumor when first seen.

To the author the most interesting facet of the survey is a study of the pathologist's report before and after radiation therapy. In this study, less change was found in the tumor in the axillary nodes than in the primary breast tumor. Only occasionally did the pathologist describe hyaline change, fibrosis, and endarteritis in the nodes. The report in 18 cases described "shrunken, atrophic, or unrecognizable tumor cells" in the breast in instances where it was known that only a segment of the tumor had been removed for biopsy. Increased fibrosis and hyalinization were seen twenty-four times, endarteritis five times, calcification once.

The use of preoperative irradiation is considered justified in that it reduces the danger of disseminating tumor cells during subsequent surgery. The author believes that modern radiologic technics may overcome former objections to preoperative irradiation and that this mode of therapy deserves a more extensive trial.

Two cases are reported.

Four tables. WILLIAM MARTEL, M.D.
University Hospital, Ann Arbor, Mich.

Effect of Alpha Particle Hypophysectomy on Disseminated Cancer of Male Breast. John D. Constable, John H. Lawrence, James L. Born, Cornelius A. Tobias, Piero E. Ariotti, Francesco F. Sangalli, Richard C. Carlson, and Paul Toch. J.A.M.A. **174:** 1720–1723, Nov. 26, 1960. (Donner Laboratory, University of California, Berkeley, Calif.)

Disseminated breast carcinoma in the male which is hormone-dependent may be controlled by surgical removal of the testis, adrenals, or hypophysis. In a preliminary report the authors discuss their experience in this condition with particulate radiation to ablate the pituitary. Protons, deuterons, or alpha particles may be accelerated to exceedingly high energies in a 184-inch cyclotron. These radiations have unusual powers of penetration and a small degree of scatter compared with conventional roentgen and gamma radiation. With a 900-million-volt beam of alpha particles from a cyclotron, depression of function and even ablation of the pituitary is possible without excessive damage to surrounding tissues.

Two patients who received alpha-particle irradiation are discussed. The first died; it is probable that the advanced stage of the disease made the time-dependent response an impossibility. In the second patient, a man with osteolytic metastases in the left femur and pelvis, hard, palpable nodes in the left supraclavicular area, and a palpable liver edge two to three fingerbreadths below the costal margin, good clinical and roentgen improvement was apparent, together with evidence of hypophysectomy after a dose of 27,000 rads, divided into six treatments over a period of eleven days. Eighteen months after irradiation there was no sign of recurrence of lymph-node enlargement and the patient was enjoying a life of normal activity.

Two roentgenograms. WILLIAM MARTEL, M.D.
University Hospital, Ann Arbor, Mich.

PREOPERATIVE RADIATION IN TREATMENT OF BREAST CARCINOMA (*Tice*)

No. Cases	Stage	Survival less than 5 yr.	Survival more than 5 yr.	Survival more than 10 yr.	Survival more than 15 yr.	Survival More than 20 yr.
13	I	1	12	9	7	5
7	II	3	5	2	2	1
16	III	10	5	3	2	1
4	IV	4	0	0	0	0
40		18	22	14	11	7

Radiotherapy in Thoracic Neoplasms. Ralph Phillips. Dis. of Chest **39:** 50–55, January 1961. (Memorial Center for Cancer and Allied Diseases, New York, N. Y.)

In a paper delivered at the Annual Meeting of the American College of Chest Physicians, the author reviews the current status of radiotherapy in thoracic neoplasms. The material is based largely on six representative reports, three from the United States and three from England. At the present time if there is no improvement in the results of treatment as given five or more years ago, out of 100 pathologically confirmed and treated cases of primary lung cancer, 10 five-year survivals from surgery and 2 five-year survivals from radiotherapy will be obtained. In the author's opinion this 12 per cent five-year survival rate could be doubled by attention to the following points:

1. In non-resectable cases, tumor-sterilizing doses of irradiation can be safely given by well planned radioactive implants at the time of thoracotomy or by the use of supervoltage x-ray and telecobalt therapy with proper dose-planning, or by a combination of the two.

2. Postoperative irradiation of the regional lymph nodes (or radioactive implants at operation) can improve the salvage rate in patients with proved metastases to the regional nodes.

3. About 80 per cent of resected lung cancers show venous invasion, and preliminary studies suggest that many patients have free-floating cancer cells in the blood stream which disappear or decrease in number following irradiation of the primary tumor. The use of preoperative irradiation in selected cases would improve present results.

4. Lung cancers which appear circumscribed radiographically are much more likely to be resectable than the non-circumscribed tumors, regardless of the particular cell type. Since radiotherapy often produces tumor regression, with better circumscription of the tumor demonstrated on the roentgenogram, more use of preoperative irradiation would again seem to be a logical step toward improving the survival rate.

5. Although chemotherapy of lung cancer is not yet by itself a curative measure, its use in combination with surgery and irradiation in both operable and inoperable cases may well improve the survival rate.

Whether or not the wider adoption of these proposals results in a higher five-year survival rate, there would certainly be an improvement in the quality of palliation and the duration of symptom-free life. "In general the best palliation is the result of an attempt to cure which fails."

Four cases are reported to illustrate the application of the above suggestions.

Nine roentgenograms; 1 photograph.

H. N. STURTEVANT, M.D.
Springfield, Mo.

Combined Therapy of Inoperable Lung Carcinoma with 5-Fluorouracil and Irradiation. Forrest M. Willett, Laurance V. Foye, Jr., Merall Roth, and Byron E. Hall. Dis. of Chest **39:** 38–41, January 1961. (VA Hospital, San Francisco, Calif.)

In an attempt to better the discouraging results in inoperable pulmonary cancer, the authors treated 16 patients with proved epidermoid carcinoma of the lung with x-ray therapy and 5-fluorouracil. The irradiation was administered at 250 kv, h.v.l. 3 mm. Cu, in daily tumor doses of 100–200 r, five days a week, to a total tumor dose of 2,000 r. The 5-fluorouracil was given intravenously over a two-to-three-hour period in 200–500 c.c. of normal saline. The course of combined therapy required two weeks for completion. The daily dosage schedule is described in detail. Five patients experienced no toxic effects. Of the remaining 11, 7 had moderately severe pharyngitis or esophagitis, involving in each instance areas within the field of irradiation. Leukopenia developed in 4 patients and thrombocytopenia in 4. Toxic manifestations were transient, disappearing within seven to ten days upon cessation of therapy.

In every patient there was unequivocal regression of the treated tumor mass within two weeks of completion of the simultaneous x-ray and 5-fluorouracil therapy. Although all cases were far advanced, several patients were alive and comfortable at the time of the report, six months after the combined treatment. One patient, considered in terminal condition when treatment was undertaken, was without complaints and without evidence of tumor after a year. It is hoped that by further study of this and other similar therapeutic combinations the prognosis in inoperable lung carcinoma may be improved.

Six roentgenograms; 1 table.

H. N. STURTEVANT, M.D.
Springfield, Mo.

Bronchogenic Carcinoma. A Second Look at Cell Type. William Umiker and A. James French. Cancer **13:** 1053–1061, September-October 1960. (VA Hospital, Ann Arbor, Mich.)

Current histopathological classifications of bronchogenic carcinoma usually include at least three cell types: squamous-cell, gland-cell, and undifferentiated-cell. The lack of standard cytologic criteria in statistical analyses has resulted in confusing differences in the reported interrelationships of age incidence, relative frequency of cell type, topography, growth patterns, resectability, and prognosis. Nevertheless, some therapeutic and prognostic implications of cell type have been well established.

The authors have investigated the practical merits of separating poorly differentiated squamous-cell carcinomas and poorly differentiated adenocarcinomas from their differentiated prototypes on the one hand and from the undifferentiated carcinomas on the other.

The age incidence, tumor size, patterns of local growth, metastases, and microscopic characteristics of 121 bronchogenic carcinomas (bronchial adenomas and bronchiolar carcinomas were excluded) were studied. All patients were male veterans from the VA Hospital, Ann Arbor, Mich. Thirty-eight of the tumors were classified as squamous-cell carcinoma; 16 as adenocarcinoma; 39, poorly differentiated carcinoma; 28, undifferentiated carcinoma. Several interesting charts and tables are presented, which show (1) that squamous-cell carcinomas most commonly excavate (about 42 per cent); (2) that adenocarcinomas and poorly differentiated carcinomas most commonly invade the pleura (about 50 per cent); (3) that poorly differentiated carcinomas produce pleural effusion most often (about 35 per cent) and most often metastasize to the nervous system (about 45 per cent). Many other comparisons are included. The well differentiated adenocarcinomas, like the squamous-cell carcinomas, were less prone to metastasize to lymph nodes than the

poorly differentiated or undifferentiated carcinomas, although this seemed to be due largely to their more peripheral location. As would be expected, the poorly differentiated carcinomas exhibited a topographical distribution and gross pathological features that were intermediate between those of squamous-cell carcinoma and adenocarcinoma. The invasiveness of undifferentiated carcinoma was well documented in the authors' material, andt he findings attested to its insidious, lethal nature.

The authors recommend the following classification: (1) differentiated carcinoma (squamous-cell and adenocarcinoma); (2) poorly differentiated carcinoma; (3) undifferentiated carcinoma (large-cell and small-cell types).

This article is basically a histopathological discussion of value to anyone interested in the broad scope of bronchogenic carcinoma.

Eight photomicrographs; 4 charts; 4 tables.

H. N. STURTEVANT, M.D.
Springfield, Mo.

Inoperable Cancer of the Bronchus Treated by Megavoltage X-Ray Therapy. Robert Morrison and Thomas J. Deeley. Lancet **2:** 618–620, Sept. 17, 1960. (Hammersmith Hospital, London, W. 12, England)

In 1957, the authors published a preliminary account of the results of treatment of inoperable carcinoma of the bronchus by megavoltage x-ray irradiation (Lancet **2:** 907, 1957) in a series of 199 cases. They now report the later progress of the same group of patients and of an additional 78 patients treated since 1957. Therapy was administered with an 8-million-volt linear accelerator. The physical characteristics of the x-ray beam produced by this machine and the clinical advantage of megavolt compared with 240-kv irradiation have been discussed elsewhere (Morrison *et al.* Brit. J. Radiol. **29;** 177, 1956. Abst. in Radiology **68:** 307, 1957).

Hemoptysis was arrested in 94 per cent of the cases; in about 75 per cent, dyspnea, pain, or cough was also relieved. Six per cent of the patients lived for five years or more. In a group of 176 patients treated with 240-kv x-rays at the same hospital, between 1949 and 1953, the three-year survival rate was 2 per cent. After three years, the risk of dying from the disease is small, and a three-year survival-rate seems to be a satisfactory index of the value of treatment in curing or controlling this disease. In squamous-cell tumors the three-year survival rate was 8.9 per cent, but only 1 patient with an anaplastic-cell tumor survived for three years. The chance of survival is best (10 per cent) in squamous-cell tumors with no evidence of mediastinal spread. The prognosis is better for patients with upper-lobe (and middle-lobe) tumors than for those with lower-lobe tumors; this same difference in survival rates in patients with tumors of the upper and lower lobes was found in those treated with 240-kv x-rays.

With megavoltage therapy there were fewer systemic and local radiation reactions than with conventional x-ray therapy, making it possible to treat larger and more extensive tumors. Radical x-ray treatment of carcinoma of the bronchus (squamous-cell type) is indicated when the tumor is inoperable in patients who are not severely debilitated and who have no evidence of spread outside the chest. Local treatment may fail because the primary growth responds incompletely or because of early dissemination of tumor cells.

One drawing; 1 graph; 6 tables.

Cell-Division in Carcinoma During Radiotherapy: A Criterion of Response to Treatment. N. B. Atkin. Lancet **2:** 778–781, Oct. 8, 1960. (Mount Vernon Hospital, Northwood, Middlesex, England)

One hundred and thirty patients with carcinoma of the cervix received an initial radium treatment by a modified Stockholm technic (one 50-mg. intrauterine tube and two 30- or 20-mg. intravaginal ovoids, *in situ* for twenty-two hours), followed in most cases by two further radium insertions (on day seven and either day fourteen or day twenty-one); in a few cases the initial radium treatment was followed by external irradiation from a Co^{60} source or a 4-Mev linear accelerator to the whole of the pelvis. Biopsy material was obtained under anesthesia, usually immediately before the second radium insertion, and was examined for the presence of cells in mitosis.

One week after the first treatment, the changes known to occur after irradiation were seen in varying degree: cellular enlargement, increase in necrosis, decrease in normal mitoses, and the appearance of abnormal mitoses. Abnormal metaphases having scattered or degenerating chromosomes or chromosome-fragments were seen in nearly every specimen, irrespective of the response. The presence of normal anaphases and telophases was clearly correlated with a poor response to irradiation, however, since in 11 out of the 13 cases in which they were found, either the tumor failed to regress or there was local recurrence within eight months.

The findings reported here have been related to the response of the primary tumor only. Although those cases that will fail through inability of the treatment to deal with extension of the tumor may not be indicated, it is possible that the presence of normal anaphases and telophases nevertheless provides an early indication of a poor local response to treatment.

Three photomicrographs; 2 tables.

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250 Kv. Rotation Therapy for Carcinoma of the Esophagus Using the Johns Hopkins Screen Intensifier. R. J. Dickson and R. H. Morgan. Am. J. Roentgenol. **85:** 78–86, January 1961. (Johns Hopkins Hospital, Baltimore, Md.)

The authors review the results of 250-kv rotation therapy in 41 cases of carcinoma of the esophagus. Accurate direction of the treatment beam and reduction of beam size to the minimum (usually 5 cm. width) needed to irradiate the entire tumor volume were facilitated by use of a televised fluoroscopic screen intensification system adopted at the Johns Hopkins Hospital (Morgan *et al.*: Am. J. Roentgenol. **70:** 705, 1953. Abst. in Radiology **63:** 458, 1954). The majority of the patients were males in the sixth and seventh decades of life. A dose rate of approximately 1,000 r per week was given in five treatment days with a calculated tumor dose of between 5,500 and 6,000 r in five to six weeks in most cases. Intraesophageal dosage measurements in 10 patients corresponded well with the values calculated by the transmitted dose method (Wachsmann and Barth: Die Bewe-

gungsbestrahlung. Stuttgart, Thieme, 1953. Reviewed in Radiology **62**: 755, 1954).

The survival time of the 41 patients is shown in the accompanying table.

250 Kv. ROTATION THERAPY FOR CARCINOMA OF THE ESOPHAGUS (*Dickson and Morgan*)

Survival Time (mo.)	Dead	Alive
Less than 6	17	..
6–12	13	3
12–24	3	2
More than 24	2	1

Average survival, all patients, 8.7 mo.; average survival, patients dead, 8.4 mo.; average survival, patients alive, 10.0 mo.

The cause of death was metastasis in 15 cases, local recurrence in 4, fistula in 5, stricture in 6, recurrence elsewhere in 4, and unknown in 1 instance. In none of those who died of metastasis was there tumor recurrence at the site of the primary lesion, and the majority of these patients were able to swallow relatively normally for the months of life remaining to them. In 1 case of stricture, resection showed evidence of dense fibrosis but no active tumor; an attempt to dilate the stricture in another patient two years after completion of therapy led to perforation and subsequent death; in the other 4, gentle dilatation of the stricture kept the lumen temporarily patent, but subsequent dilatation became increasingly necessary and the patients gradually succumbed from inanition and cachexia. In the fistulous cases which came to autopsy there was evidence of persistent tumor at the site and in 3 the fistulous openings were into closely adjacent major blood vessels. The finding of radiation pneumonitis was confined to 1 case.

It is felt that post-therapy esophagoscopy is of considerable value, although only the positive biopsy is useful in prognosis. The procedure was carried out in 14 patients; the biopsies were negative, showing only scarring, in all but 1. The patient with a positive biopsy died of his disease three months later. In all the cases a characteristic circumferential contraction of the esophageal lumen, with smooth walls, was seen. A bougie was passed through this constriction which was found to be readily distensible, and biopsies were then taken from the area below the constriction. No complications ensued from this procedure.

Four photographs; 7 tables.

PHILIP M. JOHNSON, M.D.
Montclair, N. J.

Stage I Carcinoma of the Uterine Cervix. Comparison of Results with Variations in Treatment. Frank R. Lock, Frank C. Greiss, and Damon D. Blake. Am. J. Obst. & Gynec. **80**: 984–994, November 1960. (Bowman Gray School of Medicine, Winston-Salem, N. C.)

From Jan. 1, 1943 to Dec. 31, 1948, 387 patients with carcinoma of the cervix received primary treatment at the North Carolina Baptist Hospital. The lesion was Stage I in 184 cases (47.5 per cent) and involved a cervical stump in 13 patients (7 1 per cent). In this report a comparison is made of results achieved with variations in treatment.

It was found that optimal dosage levels of pelvic irradiation as given by Nolan *et al.* (Am. J. Obst. & Gynec. **72**: 789, 1956. Abst. in Radiology **69**: 472, 1957) and Garcia (Am. J. Roentgenol. **73**: 35, 1955. Abst. in Radiology **65**: 824, 1955) may be supplemented by radical hysterectomy and pelvic lymphadenectomy for the treatment of Stage I cervical carcinoma without a prohibitive increase in complications. This combination yielded an increase in survival rate from 68.5 per cent with radiation therapy alone to 86 per cent.

Intensive pelvic irradiation probably does not improve survival in patients with cervical carcinoma, the rate of complications is unduly high, and the incidence of pelvic necrosis following subsequent radical operation is prohibitive.

Primary radical operation in selected patients yields excellent results.

Earlier diagnosis within Stage I improves survival with cancer of the cervix, but even the earliest of invasive lesions must be treated as though metastases had already occurred.

Therapy must be individualized for every woman with cervical carcinoma to obtain maximal survival with a minimum of complications. Treatment must be flexible enough to meet unforeseen problems. Therapy must be planned so that avenues of treatment for recurrent disease are not closed.

Six tables.

Long-term Follow-up Observations in Cervical Cancer. A. N. Arneson and Carol F. Williams. Am. J. Obst. & Gynec. **80**: 775–790, October 1960. (Washington University School of Medicine, St. Louis, Mo.)

During the period 1935–1954 a total of 394 patients with primary cervical cancer were examined with a view toward treatment. Ten of that number were diagnosed as having carcinoma *in situ*, and treatment was omitted for specific reasons in 10 of the patients with invasive cancer. A five- to twenty-year follow-up is reported for the remaining 374 who were treated primarily by irradiation.

This consecutive series of cases can be divided at the end of the year 1949 into two approximately equal groups. The effectiveness of treatment was tested by comparing relative five-year results for the more recently treated patients with those applying to the earlier group. Advance in survival was not demonstrated despite the fact that the percentage distribution of early lesions increased during the years in question.

The difference in results was investigated by tabulating data in accumulative survival rates. At five years observation, those values did not differ from relative results because all the patients were observed for that number of years. The accumulative rates present a more valid assessment, however, by showing the rate of accumulated deaths from cancer as well as from other causes. The lesser survival rate of patients treated in the 1950–1954 period is explained by a greater loss due to causes other than cancer and by a disproportionate incidence of cases with an unfavorable prognosis. The less favorable material is recognized by more rapidly accumulated cancer deaths during the first year of observation. Those patients were found among the Stage II cases treated in 1952 and 1953.

At more than five years observation, the accumulative survival rate fell below the corresponding relative value. The number of patients changed by a decrease

in the number not yet followed for specified periods. The accumulative survival rate fell below relative values by the weight of difference in early results upon all subsequent time intervals.

Deaths from cancer accumulate rapidly for the first two years following treatment. A realistic majority is reached by the fifth year, but there was in this series a gradual accumulation through the eleventh year. A satisfactory statement of results can be made, therefore, on the basis of the five-year values. A patient clinically well but lost to follow-up after that period has low probability of dying from cancer. The risk appears almost eliminated after the tenth year. In the observations here reported the accumulative loss to follow-up did not reach significant proportions until after the ninth year. The deaths due to intercurrent conditions also accumulated slowly but continued to expand for the total period of observation. A significant number of these were due to the development of second primary cancers. Three occurred in the rectum and 1 in the endometrium. Consideration is given to the possibility that the previous irradiation may have been an etiological factor.

Experience with programs of secondary irradiation has been unfavorable in the treatment of patients with persistent or re-appearing cancer. In more than 50 such attempts, only 2 patients survived an additional five years after the second course of therapy. Pelvic exenteration was more effective, but in 5 of the 9 attempts at operation, the disease was found too advanced. The spread of cancer is believed assessable in 123 of the 132 deaths from cancer in Stages I, II, and III. Half of that number were in patients with distant metastases with or without local disease in the pelvis. The most common sites of involvement were lung and bone. The incidence of distant spread was greatest in Stage I, which showed a rate of 66 per cent.

The effectiveness of treatment is assessed in relation to complications. Two examples are reported of late injury attributed to irradiation. Among major complications the incidence of fistula is believed to have identity with significant changes in radium treatment. The rate fell from 11 per cent in the earliest years of the report to only 2 per cent in the 1950–1954 period. This improvement is taken as evidence of advance in treatment, despite the lack of increased survival rates for the most recent years.

A statement of relative survival has weakness if used alone to compare results. The fall in survival rate for the 1950–1954 period is satisfactorily explained in accumulative tables, but it is possible that treatment was also a factor. During those years experience was accumulated in the use of specific applicators for radium treatment. There is more than speculative reason to suspect overexposure. Whatever the cause of failure, there is evidence of recovery from those defects at the end of the 1950–1954 period.

Five figures; 15 tables. AUTHORS' SUMMARY

End Results in Adenocarcinoma of the Endometrium Managed by Preoperative Irradiation. John B. Montgomery, Warren R. Lang, David M. Farell, and George A. Hahn. Am. J. Obst. & Gynec. **80:** 972–980, November 1960. (Department of Obstetrics and Gynecology, Jefferson Medical College and Hospital, Philadelphia, Penna.)

Two hundred and ninety-seven patients with endometrial carcinoma were registered in the Pelvic Malignancy Clinic of the Jefferson Medical College Hospital (Philadelphia) between Sept. 1, 1921 and Dec. 31, 1954. The follow-up was complete at the time of this report except for 2 private patients who, although not seen for two years, were not yet regarded as lost to follow-up. The five-year results are summarized in the accompanying table:

END RESULTS IN ADENOCARCINOMA OF THE ENDOMETRIUM (*Montgomery et al.*)

Treatment	Patients	Survivors
Adequate operation	20	15 (75.0%)
Inadequate operation	5	0 (0.0%)
Radium alone	46	28 (60.8%)
X-ray alone	5	0 (0.0%)
Radium plus x-ray	46	21 (45.6%)
Inadequate operation plus irradiation	15	10 (66.6%)
Adequate operation plus irradiation (not planned)	27	11 (40.7%)
Radium plus operation (planned)	120	104 (86.6%)
Total patients treated	284	189 (66.5%)
Treated elsewhere	8	4 (50.0%)
Untreated	5	0 (0.0%)
TOTAL NUMBER OF PATIENTS	297	193 (64.9%)

No striking improvement could be noted when the five-year results after 1946 were compared with earlier ones, but the record in recent years indicates considerable advance over the 39 and 55 per cent survivals previously reported from the same department. The choice of therapeutic procedures has been influenced largely by the extent of the disease, the physical condition of the patient, sometimes her lack of cooperation, and the clinical judgment of the gynecologist. Irradiation, especially with intrauterine radium, has played a prominent part in the therapy. In operable cases it has been used primarily to devitalize the carcinoma and thereby prevent manipulative spread and local recurrence. The preferred method of treatment has been intrauterine radium followed in six weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy. Sixty per cent of the cases were treated by less satisfactory methods, usually because the carcinoma was advanced or the patient was a poor operative risk.

Fifteen tables.

Selection of Treatment for Corpus Cancer. S. B. Gusberg, Herbert C. Jones, Jr., and H. M. M. Tovell. Am. J. Obst. & Gynec. **80:** 374–380, August 1960. (Columbia-Presbyterian Medical Center, New York, N. Y.)

Solution of the problems encountered in the treatment of corpus cancer would progress more rapidly if there were some classification permitting comparison and critical evaluation of material, comparable to the International Classification for Cancer of the Cervix. With this in view, 360 patients treated in the Sloane Hospital for Women and the Francis Delafield Hospital (New York) in the years 1938 to 1952 were studied from the histologic, radiotherapeutic, and surgical points of view. From this study it appears that one might formulate a set of principles for treatment of corpus cancer

based on present knowledge of the disease in the following way:

Stage I: A minimal lesion well differentiated and local, with a small uterus, offers a situation in which total hysterectomy alone gives as good a result as a combined technic.

Stage II: The moderate lesion with the uterus up to the size of a two- and one-half month pregnancy (or smaller with an undifferentiated tumor) will be benefited by preoperative radium application by the Stockholm method or a modification thereof, followed by extrafascial total hysterectomy. The majority of corpus cancers fall into this group.

Stage III: The advanced lesion with a large uterus (or one of moderate size with an undifferentiated tumor) and/or cervical, vaginal, or parametrial involvement may permit a choice of treatments according to the suitability of the patient as a surgical candidate and according to technical considerations: (*a*) radical hysterectomy; (*b*) preoperative radium therapy followed by extended total hysterectomy and node dissection; (*c*) preoperative x-ray therapy and total hysterectomy.

Stage IV: With involvement of the bowel or bladder, or distant metastases, treatment must be individualized. Total pelvic exenteration might salvage an occasional patient.

All Stages: Postoperative x-irradiation may be given patients with involvement of the cervix, parametrium, or ovary, with deep myometrial penetration of the tumor, or with overt pelvic node disease.

Eleven tables.

Primary Cancer of the Ovary: An Analysis of 349 Cases. Stanley W. Kent and Donald G. McKay. Am. J. Obst. & Gynec. **80:** 430–438, September 1960. (Free Hospital for Women, Brookline, Mass.)

Three hundred and forty-nine women with previously untreated primary cancer of the ovary have been patients at the Free Hospital for Women, Brookline, Mass., from 1904 through 1952. A report based on the 238 treated before 1943 has been published by Allan and Hertig (Am. J. Obst. & Gynec. **58:** 640, 1949. Abst. in Radiology **55:** 470, 1950). From Jan. 1, 1943, to Dec. 31, 1952, there were an additional 111 new patients with primary ovarian cancer. Both groups have been combined in a single study, which is presented in this report.

An attempt was made to isolate the important prognostic factors and, when possible, to study the behavior of the various microscopic types. Grading of the tumors microscopically was of value both in prognosis and in predicting the response to radiation. The well differentiated tumors and those thought to represent borderline malignancy were designated Grade I. The Grade II tumors contained complex epithelial papillae but had little or no solid epithelial growth. Those with a solid or almost solid histologic growth pattern and a high percentage of undifferentiated cells were considered Grade III. A few tumors were not graded because of unusual and atypical appearance. The clinical staging classification was that originally proposed by Munnell and Taylor (Am. J. Obst. & Gynec. **58:** 943, 1949. Abst. in Radiology **55:** 633, 1590): Stage I, cancer limited to one ovary; Stage II, cancer limited to both ovaries; Stage III, cancer involving other pelvic viscera or pelvic peritoneum; Stage IV, cancer involving structures above the pelvis.

The effectiveness of postoperative x-irradiation was demonstrated. Immediate postoperative irradiation was given to the pelvis and lower abdomen as part of the definitive treatment of 154 patients; 173 survived the postoperative period but received no irradiation. The five-year salvage rates in the first group were 45.5 per cent; in the second group 32.9 per cent. This difference is significant. With definitive operation alone, the five-year survival was 37 per cent; in 117 patients who received definitive operation plus x-irradiation, the five-year salvage rate was 53 per cent. Conventional therapy was employed: 200 kv with 0.5 mm. copper screening and a target distance of 50.0 cm. No patient in this series was exposed above the level of the umbilicus. Portals of entry were 10 × 15 or 15 × 15 cm., both front and back, usually two to the lower quadrants and one to the lower back. The number of exposures varied twelve to twenty. Total doses at the skin level varied from 3,000 to 9,000 r, and dosages delivered to the midpelvic plane ranged from 1,400 to 2,600 r.

Although x-irradiation resulted in some apparent improvement in five-year survival in all grades of tumor, the most marked difference was seen in Grade III tumors where a threefold increase in survival followed irradiation. Pseudomucinous tumors showed no radiation response, while serous and undifferentiated carcinomas responded well. There was an increase in survival with x-ray treatment in Stage I and Stage III cases but no improvement in Stage IV cases.

The best results were obtained when the uterus, ovaries, and as much of the tumor as possible were removed and x-irradiation was given postoperatively. The benefits of radiation are maintained to the twenty-year level in both early and late ovarian cancer. With the exception of the endometriocarcinomas, the miscellaneous types carry a less favorable prognosis than the serous and pseudomucinous types.

Three figures; 14 tables.

Wilms's Tumor: A Review of 47 Cases. A Discussion of the Findings and Results of Treatment of Histologically Proved Cases in a 15-Year Period. Raymond C. Kinzel, Stephen D. Mills, Donald S. Childs, Jr., and James H. DeWeerd. J.A.M.A. **174:** 1925–1929, Dec. 10, 1960. (Mayo Clinic, Rochester, Minn.)

The case records of 85 patients seen at the Mayo Clinic in the period 1941 through 1955 with a clinical or preoperative diagnosis of Wilms's tumor were reviewed. In 47 of these the tumor was histologically proved, giving an incidence for the fifteen-year period of 1 per 20,000 admissions.

A palpable abdominal mass, the most common complaint, was present in 33 of the 47 cases, abdominal or flank pain in 14, fever in 7, gross hematuria in 6, and nausea and vomiting in 1. The abdominal mass was usually smooth, fixed, and in most cases palpable to the midline and to the rim of the ilium.

In 32 of 36 cases in which excretory urograms were available, there was definite evidence of an expanding renal mass. (The authors cannot agree that retrograde urography, on the other hand, should always be performed, but prefer to use it only in selected cases.)

Twenty-two of the 47 patients were under three years of age; 23 were three to thirteen; 2 were adults aged thirty-two and fifty-three. The cases were about equally divided as to sex (25 female; 22 male) and laterality of the lesion (25 on the right; 22 on the left). Metastases were primarily to the lung (14 cases);

otherwise to the renal fossa (4 cases), pelvis (3 cases), liver (2 cases), and eye, cervical nodes, and bladder (once each).

The most effective treatment consisted of preoperative irradiation, nephrectomy, and postoperative irradiation, this program yielding a three-year survival rate of 57 per cent. Invasion of the renal capsule, tumor in the renal veins, and large tumors (over 300 grams) affected the prognosis adversely. The most important prognostic factor was found to be the age of the patient: the three-year survival rate was 37 per cent in the total series of 43 traced patients, 44 per cent on the basis of the 36 operable patients, and 67 per cent for those under two years of age at the time of diagnosis.

One chart; 2 tables.

RICHARD H. GREENSPAN, M.D.
Yale University School of Medicine

Attempts at Transplantation of Human Bone Marrow in Patients with Acute Leukemia and Other Marrow Depletion Disorders. Farid I. Haurani, Evalyn Repplinger, and L. M. Tocantins. Am. J. Med. **28:** 794–806, May 1960. (Jefferson Medical College, Philadelphia 7, Penna.)

Twenty-six attempts at transplantation of human bone marrow obtained from excised bones were carried out in 19 patients with acute leukemia and other marrow depletion syndromes with or without preliminary total-body radiation. There was no evidence of a permanent "take" after any of the attempts, although signs of transient functioning of the marrow appeared in 3 instances.

Four additional patients received marrow *aspirated* from living donors (2 homologous and 2 autologous). One patient with reticulum-cell sarcoma underwent a relatively long remission after receiving 100 mg. of nitrogen mustard, followed by injection of her own preserved marrow.

The course of the patients with acute leukemia did not in general seem to be altered significantly by radiation and injections of marrow. The explored sources of procurement and methods of processing and administering marrow from excised bones may provide a basis for the utilization of human marrow in future attempts to transplant bone marrow.

Six figures; 7 tables.

Liposarcoma. A Clinical and Pathological Study of 53 Cases. Horatio T. Enterline, John D. Culberson, Donald B. Rochlin, and Luther W. Brady. Cancer **13:** 932–950, September-October 1960. (Hospital of University of Pennsylvania, Philadelphia 4, Penna.)

Although liposarcoma is not the most common malignant soft-tissue tumor, it is perhaps the most important, since prompt diagnosis and adequate treatment should result in a relatively high salvage rate. The findings in 53 cases studied at the Hospital of the University of Pennsylvania during the period 1940–1957 are tabulated.

Liposarcoma must be differentiated from a variety of benign neoplasms, inflammatory conditions, and lesions of uncertain nature. Some of these are discussed, including fat necrosis, malignant fibrous xanthoma, xanthogranuloma, and pseudosarcomatous fasciitis, myxoma and myxosarcoma, localized myxedema, and benign fatty tumors.

The behavior of liposarcoma varies widely, and these variations are closely related to its histologic structure. The authors recognize a well differentiated pure myxoid type, a poorly differentiated pure myxoid type, a lipoma-like type in which all or part of the tumor closely mimics normal fat, a myxoid mixed type, and a non-myxoid type.

Liposarcoma is rare in patients under thirty years of age. The average age in the the present series was fifty-three years. The tumor shows a marked predilection for the thigh and the retroperitoneum. Twenty-two of the authors' cases originated in the lower extremity from knee to buttock. Eleven of the 53 patients had more than one tumor.

Local recurrence was related to size of the mass and was invariable after known or suspected incomplete excision, usually within three years. Metastases developed in 31 per cent of the cases. In all but 1 of these the primary lesion was larger than 5 cm. Eighty-six per cent of the patients with the non-myxoid type of tumor had metastases within five years; only 2 of the 27 pure myxoid and "lipoma-like" tumors metastasized.

No one has advocated irradiation as an initial procedure aimed at definitive cure of liposarcoma. Primary irradiation has been reserved for those cases deemed inoperable. It is found useful in palliation when the tumor is largely myxoid in structure. It appears ineffective in the nonmyxoid type.

Some aspects of surgical therapy are discussed. The overall survival in the present series, without evidence of residual tumor, was 32 per cent at five years and 28 per cent at ten years. Survival was much higher for patients with the purely myxoid tumors (57 per cent and 66 per cent) than for those with the non-myxoid and mixed types (12.5 per cent and 8.3 per cent).

Eleven photomicrographs; 12 tables.

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The Use of Standard Isodose Distributions with High Energy Radiation Beams—The Accuracy of a Compensator Technique in Correcting for Body Contours. E. J. Hall and R. Oliver. Brit. J. Radiol. **34:** 43–52, January 1961. (Radiotherapy Department, Churchill Hospital, Oxford, England)

In order to make use of standard isodose charts, the irregular outline of the patient is converted to a plane surface at right angles to the central axis of the radiation beam by a metal compensating filter placed some distance from the skin. The errors and limitations of this system stem from inaccuracies due to (1) the geometry of the technic, assuming a point source of radiation; (2) the finite size of the source; (3) the use of a stepped compensator with a source of finite size and with a point source.

The use of metal compensators mounted at 20 cm. from the skin has proved a simple and practicable method of correcting for the irregularity of the patient's contour in high-energy radiotherapy. The full skin-sparing advantage of high-energy radiation is preserved, and at the same time the standard isodose curves can be applied directly to determine the dose distribution within the patient.

Compensators are made so that the thickness of aluminum parallel to the direction of the central ray is equal to $0.88\,h/p$ where h is the corresponding thickness of unit density material replaced and p is the density of the aluminum. This compromise provides satisfactory compensation for the conditions of normal clinical

use. At a depth of 5 cm. in a patient, the dose will not be in error by more than ±2 per cent for the whole range of field sizes and amount of compensation encountered. At the same time, dose at the surface will not be more than 0 to 5 per cent low, and at a depth of 10 cm. not more than 0 to 5 per cent high.

To avoid errors resulting from the geometry of the system, the density of the compensator material should have the optimum value given by the expression $p = 0.88\, b/a$, where b is the source-skin distance of the particular unit and a is the distance from the source at which the compensator is mounted.

In practice it is convenient to use a material such as aluminum or brass, because it is easily machined and compensator pieces can be cleaned and re-used indefinitely. The additional errors of compensation introduced by the use on the authors' unit of aluminum instead of a material with an ideal density do not exceed ±4 per cent for the vast majority of cases met with in clinical practice. The use of brass results in somewhat larger errors.

For a cobalt unit with a source 2 cm. in diameter, compensators may be built up from a stock of aluminum columns, 3/8 in. square section, available in 12 standard lengths, in steps equivalent to 1 cm. of tissue. This provides a sufficiently fine compensation, with up and down variations in transmitted dose of only a few percentage points from the ideal continuous compensator. The cross section of the columns would need to be reduced for use with a machine with a point source.

The effect of beam divergence cannot be ignored for units working at 60 or 80 cm. source-skin distance, with compensators mounted 16 to 20 cm. from the skin, without introducing appreciable errors for steeply sloping contours. The compensator should be scaled down to allow for its position in the beam.

An experimental check of the accuracy of these conclusions showed excellent agreement except at small depths where doses are low due to the lack of local scatter.

Eight figures; 4 tables. LUCILLE DU SAULT
The Henry Ford Hospital

RADIOISOTOPES

I^{131} Plasma and Thyroid Levels in Cancer and Control Patients. K. G. Scott, W. A. Reilly, and G. L. Searle. Cancer **13:** 1261–1264, November-December 1960. (University of California School of Medicine, San Francisco 22, Calif.)

An investigation was made of the distribution of I^{131} in the presence of cancer to determine if a greater than normal retention of I^{131} could be demonstrated. Forty-three patients with cancer were included in the study. The size of the tumor was estimated in 31 instances after surgical removal, in 3 at autopsy, in 2 by palpation and by roentgenogram, and in 7 by roentgenogram only. The patients were divided into three groups according to the weight of the tumor. All were given 50 to 100 μc of carrier-free I^{131} by mouth. Controls were euthyroid, noncancerous hospitalized patients who had been given I^{131} to evaluate thyroid function.

The mean plasma iodide-131 levels of all three groups of cancer patients were significantly higher than those of the controls at both twenty-four and forty-eight hours after I^{131} administration, while the thyroid I^{131} levels of the cancer patients were significantly lower than those of the controls. The deviation from the controls was proportional to the size of the tumor.

Three tables.

A Diagnostic Radioiodine Uptake Test in Patients Receiving Antithyroid Drugs. I. D. Thomas, T. H. Oddie, and J. Myhill. J. Clin. Endocrinol. **20:** 1601–1607, December 1960. (Royal North Shore Hospital of Sydney, Crows Nest, N. S. W., Australia)

In 74 patients uninfluenced by thyroid-affecting medication, the fraction of an intravenously injected tracer dose of I^{131} present in the thyroid region ten minutes after injection (N_{8-15}) was calculated and plotted against the one-hour uptake rate. The curve thus obtained was used as a calibration curve in subsequent studies. Forty-one patients were studied under two or more of the following regimens: (i) untreated; (ii) receiving a full course of antithyroid drug treatment; (iii) receiving a thyroid hormone preparation in "suppressive" dosage; (iv) receiving a combination of (ii) and (iii). Multiplying the ten-minute thyroidal I^{131} uptake rate in a patient receiving antithyroid drugs by a factor of 1.22 yields the basic untreated one-hour uptake rate. The ten-minute uptake rate is suppressible by a thyroid hormone preparation in nonthyrotoxic patients but is not suppressible in thyrotoxic patients.

One figure; 1 table. AUTHORS' ABSTRACT

Antibodies to Thyroglobulin in Patients with Thyrotoxicosis Treated with Radioactive Iodine. C. R. Blagg. Lancet **2:** 1364–1365, Sept. 24, 1960. (General Infirmary, Leeds, England)

Serum from three groups of patients with thyrotoxicosis was investigated: (1) 102 patients with thyrotoxicosis confirmed by tracer studies, attending for treatment with I^{131}; (2) 103 patients who were euthyroid after I^{131} therapy; (3) 58 patients with a clinical diagnosis of hypothyroidism after administration of I^{131}. The isotope dosage was intended to give 7,000 to 10,000 r to the thyroid gland in fourteen days.

A significantly higher incidence of circulating antithyroid antibodies was found in the last group of patients. Auto-antibodies were demonstrated in 53 (52 per cent) of the patients withpre -therapy thyrotoxicosis, in 57 (55 per cent) of those euthyroid for a minimum of a year after the last treatment, and in 45 (77 per cent) of those with post-therapy hypothyroidism. It would seem, however, that the antibodies themselves are not directly responsible for the development of hypothyroidism. Their presence may indicate some underlying abnormality, disposing in some cases to ultimate destruction of the thyroid. The occurrence of these antibodies in the low titre usually observed in these cases is not a contraindication to radioactive-iodine treatment of thyrotoxicosis. These patients are usually over the age of forty and, if hypothyroidism develops, replacement therapy with thyroxine is cheap, easy, and safe.

The precipitin reaction should distinguish between hyperthyroid patients and those with early Hashimoto's thyroiditis who present with thyrotoxicosis.

One chart; 2 tables. HAROLD A. SWANSON, M.D.
Calgary General Hospital, Calgary, Alta.

Uptake of L^{131}-l-Triiodothyronine in Various Erythrocyte Abnormalities. O'Neill Barrett, Jr., Ann Berman, and John G. Maier. J. Clin. Endocrinol. **20:** 1467–1473, November 1960. (Walter Reed Army Medical Center, Washington, D. C.)

This study was undertaken to determine whether the erythrocyte uptake of I^{131}-L-triiodothyronine is affected by various erythrocyte abnormalities and whether consistent variations occur in association with several abnormal hematologic conditions. Plasma protein-bound iodine levels were determined in most cases in an attempt to rule out unsuspected thyroid disease. Normal I^{131}-L-triiodothyronine uptake values ranged from 10.58 to 18.34 per cent. In 3 cases of sickle-cell trait, normal values were observed, whereas in 2 pregnant patients with the trait, uptake values were low. Normal uptakes were also recorded in 1 case of sickle-cell anemia, 1 of sickle-cell thalassemia and 3 of thalassemia trait. Varying results were obtained in 9 cases of hemolytic anemia; in 2 cases associated with acute leukemia the uptakes were elevated despite very low hematocrits; in 3 cases associated with Hodgkin's disease, normal uptakes were noted in 2 and an increased uptake in 1; values were normal in a case of congenital spherocytic hemolytic anemia and elevated in a case of congenital hemolytic anemia with unusual inclusion bodies. Uptakes were elevated in 6 of 8 cases of polycythemia vera, and the value was high-normal in the seventh. Although variations in hematocrit have been shown to affect erythrocyte uptake, this factor did not account for the elevations in this group. No correlation between erythrocyte uptake of I^{131}-L-triiodothyronine and hematocrit could be made in the cases of polycythemia vera or in the cases of hemolytic anemia with elevated uptake values.

Four figures; 1 table. AUTHORS' ABSTRACT

The In Vitro Resin Sponge Uptake of Triiodothyronine-I^{131} from Serum in Thyroid Disease and in Pregnancy. Marvin L. Mitchell, Anne B. Harden, and Mary E. O'Rourke. J. Clin. Endocrinol. **20:** 1474–1483, November 1960. (Lemuel Shattuck Hospital, Boston, Mass.)

A procedure has been devised which measures the uptake of I^{131}-labeled triiodothyronine (T_3-I^{131}) from serum *in vitro* by means of a resin sponge. The sponge, consisting of a mixture of polyurethane foam and a finely divided anion exchange resin (Amberlite IRA-400), was equilibrated with serum containing T_3-I^{131}. Significant differences in the sponge uptake of T_3-I^{131} from serum were demonstrated in hyperthyroidism, myxedema, and uncomplicated pregnancy when compared with the sponge uptake from the serum of normal subjects; values were elevated in hyperthyroidism and reduced in pregnancy and myxedema. Augmented sponge binding of T_3-I^{131} was also observed following the administration of thyrotropin to subjects other than those with primary myxedema. The results indicate that the resin sponge procedure may be a useful means for distinguishing between certain thyroidal abnormalities and for recognizing pregnancy and pregnancy complicated by hyperthyroidism.

Eight figures; 1 table. AUTHORS' ABSTRACT

Moving-Beam Therapy with Cobalt 60: Its Adaptability to the Lesion Shape to Be Treated. Jane Howarth and C. W. Wilson. Am. J. Roentgenol. **85:** 53–58, January 1961. (Westminster Hospital, London, S.W. 1, England)

Although some consider that the use of a moving beam adds little to the intrinsic value of supervoltage therapy, the authors have become persuaded, after nearly two years of experience with moving-beam supervoltage therapy with a cobalt-60 beam, of the distinct clinical advantage of this technic. If sufficient attention is given to the physical planning, it is possible to achieve a very wide controlled range of dose-contour patterns. Prerequisite to realization of any planned course of moving-beam therapy is a suitable, accurate, anatomic contour of the patient, reproduced on paper, with the area to be treated precisely marked within the contour.

A series of moving-beam technics for treating a variety of disease sites of different areas and shapes, achieved by individual patient planning, is described. The aim is to include the area to be treated as accurately as possible within the 80 per cent dose contour, where 100 per cent is the maximum dose delivered within the treated area.

Several examples are presented of treatment plans for eccentric or multifocal lesions. In each instance judicious selection of rotation arc lengths and of common or multiple rotation centers permits delivery of an adequate, homogeneous tumor dose.

One photograph; 8 isodose curves.

PHILIP M. JOHNSON, M.D.
Montclair, N. J.

An Experiment in the Use of Radioactive Gold for Cervical Cancer. E. Stewart Taylor, N. Paul Isbell, and Robert E. Dean. Am. J. Obst. & Gynec. **80:** 899–904, November 1960. (University of Colorado School of Medicine, Denver 20, Colo.)

Forty-four unselected patients were treated for invasive cervical carcinoma. Radioactive gold and radium were administered to alternate patients while the others of the series received traditional radium and roentgen treatment. The errors inherent in clinical staging methods are presented, and results of therapy in the two groups of patients are analyzed. Injection of parametrial tissues with colloidal radioactive gold in solution was associated with a 67 per cent rate of delayed major complications, three times the complication rate in the second group of patients. Four to six years later only 19 per cent of the patients treated with radioactive gold and radium were alive and well as compared to 48 per cent of the 23 control patients with a comparable extent of disease, treated with the traditional radium and x-ray methods.

The authors do not recommend that radioactive gold be used in the treatment of cancer of the cervix and they have discontinued its use for this purpose in their clinic. It appears to be less effective than external deep x-ray therapy as a supplement to radium in these neoplasms.

Three tables.

The Radio-Renogram, with Radio-Renografin-I^{121}, as a Diagnostic Aid in Urologic Problems. Arthur F. Abt and Vincent A. Balkus. J. Urol. **85:** 95–102, January 1961. (VA Center, Martinsburg, W. Va.)

Employment of tagged iodinated opaque media has resulted in a new diagnostic renal function test. Radio-Renografin-I^{131} (20 μc I^{131} per milliliter) is excreted, like creatinine, by way of the glomeruli. Unlike Diodrast-

I^{131}, it has the advantage of not being concentrated by the liver. This eliminates confusion, particularly for curves made over the right kidney. No initial priming dose is necessary as with Diodrast and toxicity is less because of the smaller dose.

The technic of obtaining a radio-renogram is simple. The injection is made intravenously following the placement of two scintillation probes over the kidneys which were previously outlined radiographically, and thirty-minute tracings are simultaneously recorded for both kidneys by two rectilinear recorders. On the curves obtained, the "vascular segment" due to kidney radioactivity is represented by an initial rapid rise shortly after the injection, and the "excretory segment" by the gradual slope of the curve over the thirty-minute period. In the patient with normal function, the curves of the two kidneys should be superimposed. A difference in the two curves, such as a lower vascular segment or a flattened excretory segment, indicates unilateral renal disease.

Illustrations show the curves for normally functioning kidneys, as well as for unilateral malfunction due to obstruction, for renal artery disease resulting in hypertension, and impaired unilateral renal function consequent to an old infectious process.

While the dose administered for the radio-renogram is considerably smaller than that for excretory urography (1 ml. as against 20 to 30 ml.), care should be taken to protect the patient, and emergency measures should be readily available in case of serious reaction. Severe allergies and asthma are contraindications.

The method seems to afford useful information regarding renal function, detecting differences between the kidneys that would not be evident on the intravenous pyelogram. Its chief value lies in the cross-comparison of one kidney with its mate. The test compares favorably with other conventional renal function tests, but should not be considered definitive, as it can only indicate disparity in function and not the etiologic condition.

Nine figures. ROBERT E. CAMPBELL, M.D.
University of Pennsylvania

Clinical Experience with a New Test Agent for the Radioisotope Renogram: Sodium Ortho-Iodohippurate-I^{131} (Hippuran-I^{131}). Chester C. Winter, Robert A. Nordyke, and Manuel Tubis. With the technical assistance of Cecelia Kennedy. J. Urol. **85:** 92–94, January 1961. (University of California Medical Center, Los Angeles, Calif.)

The authors report their experiences with Hippuran-I^{131} as a test agent in obtaining radioisotope renograms. Unlike Diodrast-I^{131}, it has no demonstrable liver uptake and is cleared from the blood faster than Hypaque, Miokon, or Renografin-I^{131}. Its more rapid clearance results in a decrease in the time required for the test by as much as one-third. A biological half-life of twenty minutes is reported, and recovery of the administered I^{131} in the urine at the end of thirty minutes is as high as 75 per cent.

Hippuran-I^{131} has now been used in a sufficient number of patients with normal and diseased kidneys to be judged favorably as fulfilling the present criteria of an optimal test agent. It is a stable, heat-resistant, easily manufactured, commercially available, and nontoxic in the minute amounts used for the test.

Five characteristic renograms made with this new test agent are reproduced. H. W. SCOTT, M.D.
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Placental Localization with Use of Radioactive Iodinated Human Serum Albumin. Milton Shoss and Paul E. Kratz. Am. J. Obst. & Gynec **80:** 1168–1172, December 1960. (Cape Girardeau, Mo.)

In this paper the authors present a preliminary report on placental localization with the use of a radioactive iodinated human serum albumin. During the early stages of the series as little as 2 5 to 3.0 μc was injected, but with this amount the differential in the counts over the uterus and the heart was so small as to make localization of the placenta difficult. It is felt that 5 μc is more desirable and more accurate. Counts were obtained over 12 areas on the uterus and also in the right and left flanks with the collimator almost perpendicular to the spine in both of these areas.

Results in 20 cases in which localization was done by isotope counting and compared with actual findings at cesarean section or after manual removal show that in the horizontal localization 4 results were totally incorrect, 7 were slightly incorrect, and 9 were correct; in the vertical localization 1 was incorrect, 19 were correct. It is felt that the one error in vertical localization probably could have been avoided by the use of sufficiently active isotopes.

From this small series, however, the authors feel that the additional readings obtained in the right and left flank areas gave a better insight to an anterior, posterior, or lateral lying placenta, and that the additional counting areas should add to the accuracy of the procedure as a larger number are performed. The test should complement but not replace existing methods of placental localization, including x-ray examination.

The study is still in progress and a subsequent report will be made when the series reaches statistical validity.

Two figures; 1 table.

Isotope Localization of the Placenta in Suspected Cases of Placenta Previa. R. D. Visscher and W. S. Baker, Jr. Am. J. Obst. & Gynec. **80:** 1154–1160, December 1960. (Obstetrical and Gynecological Service, United States Naval Hospital, San Diego, Calif.)

The authors report their experience with the isotope technic in localizing the placenta. Only those patients admitted for third trimester bleeding or for elective repeat cesarean section were included in their investigation. Radioiodinated human serum albumin (10 μc at first; later 5 μc) was injected into the antecubital vein of those selected for study, and a scintillation detector with a sodium iodide crystal and wide-angle aperture was used to detect the gamma radiation emanation from the isotopes. Neither columnation [collimation?] nor lead filters were employed.

The placental site was accurately localized in each of the 28 patients who were subsequently delivered by cesarean section. Of the 23 patients studied with third trimester bleeding, this was due in 7 to placenta previa. In 15 of the 23 cases the placenta was shown to be in the fundus and in 7 cases in the lower uterine segment. In 1 instance an equivocal result occurred. The placental site was thought to be in the fundus, but manual exploration after a normal labor and delivery showed it to encroach upon the lower uterine segment.

The authors conclude that radioisotope localization of

the placenta appears to be a simple, safe method for the detection of cases of placenta previa and, from the results of their study, highly accurate. The conservative management of cases of placenta previa can now be pursued on a more substantial footing, thereby eliminating the need for prolonged hospitalization in certain instances where the diagnosis is uncertain. As compared with roentgen placentography, this method carries a lower radiation hazard to the mother and baby.

In an Addendum, the authors state: "Since this article was submitted for publication, the placenta has been correctly localized by this isotope technic in 47 additional cases, including 4 patients with placenta previa. This brings the total number of cases studied to 98, with 12 patients having placenta previa. The placenta was correctly localized in the fundus or lower uterine segment in each instance."

Five figures; 1 table.

Plasma Levels, Urinary Excretion, and Increase in Body Burden of Strontium-90 in Man. Joseph Samachson. Radiation Res. **13:** 192–204, August 1960. (Montefiore Hospital, New York, N. Y.)

Data obtained from the administration of a single dose of Sr^{85} have been applied to the case of daily ingestion of Sr^{90}. On the basis of various intake levels of daily Sr^{90} ingestion, the data were used to calculate possible values for excretions, body retentions, and plasma levels of Sr^{90} in human patients. By means of the relations found between Sr^{85} and Ca metabolism, the values of Sr^{90} for most individuals can also be obtained from urinary calcium excretion, without need for Sr^{85} studies. Values for body retention are in line with those found by Sr^{90} analysis of bone samples. A wide range of body retentions can occur in adults even on a single dietary Sr^{90} intake as a result of differences in metabolism of Sr and Ca from one individual to the next. Variations of dietary intake further increase the range of body retentions.

Two methods have been used for the calculation of Sr^{90} plasma levels. Both indicate that, on a given Sr^{90} intake, plasma levels of Sr^{90} vary relatively little in different individuals or from children to adults. Sr^{90} plasma levels do vary, however, directly with Sr^{90} intake and on an intake of 5 $\mu\mu$c of Sr^{90} per day are of the order of 0.10 $\mu\mu$c/l plasma.

Four tables. AUTHOR'S SUMMARY

Measurement of the Dose in Small Tissue Volumes Surrounding "Point" Sources of Radioisotopes. Patricia McClement Failla and Gioacchino Failla. Radiation Res. **13:** 61–91, July 1960. (G. F., Argonne National Laboratory, Argonne, Ill.)

An experimental investigation of the integral doses received by small spherical volumes of tissue from centrally located point sources of radioactive material is described. The radioactive isotopes used were P^{32}, I^{131}, and S^{35}.

An indirect method had to be developed to measure the energy absorbed in volumes of tissue with dimensions of the order of microns. It is shown that the conditions necessary for the determination of the dose in a cell can be established by expanding the tissue into a gas so that all linear dimensions are increased in the ratio of the density of the tissue to that of the gas. In order to make the results of measurements in a gas applicable to "solid" tissue, the measuring volume of gas (which represents the tissue volume of interest) must be the same in composition and density and continuous with the gas that represents the surrounding tissue medium. New types of ionization chambers were developed to satisfy these conditions.

These so-called "wall-less" ionization chambers have approximately spherical collecting volumes, defined by lines of force rather than material walls. The tips of two 1-mm. rods and a very thin plastic film on which the source may be deposited are the only solid materials in the collecting volume, and the effect of the film can be estimated by varying its thickness. The collecting volume, thus, is surrounded by a medium of the same composition and density, and the conditions obtaining in a tissue are thereby reproduced. The effective radius or size of the collecting volume can be changed by varying the gas pressure. The results of such ionization measurements in nitrogen were converted into terms of energy absorbed in tissue of specific composition by using known conversion factors.

The results for each isotope in absolute units are presented for spherical tissue volumes with radii up to about 200 μ in both integral and differential (*i.e.*, point source dose function) forms. Some of the biological applications of the results of the investigation are indicated.

Fifteen figures AUTHORS' SUMMARY

Irradiation of the Intestine by Radioisotopes. M. F. Sullivan, P. L. Hackett, L. A George, and R. C. Thompson. Radiation Res. **13:** 343–355, August 1960. (Hanford Laboratories, Richland, Wash.)

The gastrointestinal tract has been considered the critical organ in calculating permissible exposure limits for many radioisotopes. There is available, however, little experimental evidence of actual intestinal damage from ingested radioisotopes. The authors previously reported findings indicating the ineffectiveness of ingested α-emitters in causing damage to the gastrointestinal tract of rats (Nature **180:** 651, 1957). They now present a further elaboration on the effects of the ingested α-emitter, Pu^{239}, and describe the damage resulting from the ingestion of the β-emitting isotope Y^{91}. These changes are compared with those obtained in a previous experiment involving x-irradiated rats.

The LD 50 for orally administered Y^{91} in the rat was determined to be about 17 mc/kg. The average survival time was 8.4 days. The calculated radiation dose from this amount of yttrium to the various segments of the intestine is: small intestine, 1,150 rads; ascending colon, 2,800 rads; descending colon, 4,700 rads.

Lymphocytopenia, granculocytosis, and a mild anemia occurred after oral doses of Y^{91}. Fluid loss and hemorrhage were contributing factors to these changes.

Pathologic changes due to Y^{91} were primarily present in the large intestine owing to longer retention of intestinal contents in that segment. Damage was qualitatively similar to that observed previously after x-irradiation.

Quantities as high as 230 mc/kg. of the α-emitting isotope Pu^{239} were administered by gavage to rats without causing death. A series of animals sacrificed at three, six, and nine days displayed only superficial epithelial damage at three days. No other evidence of injury was detected.

Eleven figures.

Median Lethal Dose for Guinea Pigs of Cobalt-60 Gamma Irradiation. William T. Newton and Michel

Ter-Pogossian. Radiation Res. **13:** 298–304, August 1960. (Washington University School of Medicine, St. Louis, Mo.)

Determination of the thirty-day acute median lethal dose of cobalt-60 γ-rays for guinea-pigs was undertaken to provide reference data in the investigation of the effects of irradiation of the blood of this species by ionizing radiation emitted by radioactive oxygen-15.

The animals to be irradiated were enclosed in a Lucite cylindrical container approximately 7.5 cm. in diameter and 17.5 cm. long. The cobalt source was rotated about the axis of the container resting on the aluminum table of the radiation unit. The speed of rotation was of the order of 400° per minute, and the time of irradiation varied from fifteen to twenty minutes.

The acute thirty-day median lethal dose was found to be 326 rads in the guinea-pigs studied.

The animals tended to die nine to fourteen days after irradiation. The median life span of those dead before thirty days was twelve days. For the first nine days after irradiation the mean weight change relative to the preirradiation weight of the animals who died did not differ from the changes in the survivors. Shortly before death the average relative weight of the dying animals fell precipitously. The variation in the weight response was such, however, that in a few individuals body weight was increasing immediately before death. Weight loss began at the same time in all animals whether destined to live or die. The degree of weight loss of the surviving group during this time appeared to be related directly to the amount of radiation absorbed.

Extravasation of blood into viscera and serous cavities was the most frequent finding at autopsy.

Five figures; 1 table.

Cell Division in Endochondral Ossification. A Study of Cell Proliferation in Rat Bones by the Method of Tritiated Thymidine Autoradiography. N. F. Kember. J. Bone & Joint Surg. **42-B:** 824–839, November 1960. (Royal Cancer Hospital, London, England)

The author describes the pattern of tritiated thymidine labeling in the cells of the epiphyseal cartilage and metaphysis of the tibia of the rat at intervals of one hour to twenty-eight days after injection. The standard dose administered to each animal was 25 microcuries of tritiated thymidine in 0.5 milliliter of saline at a specific activity of 1.6–1.9 curies/m Mol. Injections were given intravenously or intraperitoneally. The region of dividing cells is defined and evidence is given for a zone of reserve cells at the top of the cartilage columns. The difficulties of quantitative grain count studies are discussed, and some approximate values are given for the generation time and mitotic cycle periods of the cartilage plate cells. Some further evidence is given about the life cycles of the osteoblast and the osteoclast.

Ten photomicrographs; 5 graphs; 1 table.

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RADIATION EFFECTS—PROTECTION

Radiation Leukemogenesis. An Analysis of the Problem. E. P. Cronkite, William Moloney, and V. P. Bond. Am. J. Med. **28:** 673–682, May 1960. (Medical Research Division, Brookhaven National Laboratory, Upton, N. Y.)

The authors state that the primary purpose of this paper is to re-examine, in the light of present knowledge, the several sources of human data bearing on the problem radiation leukemogenesis in an effort to determine to what degree predictions of the incidence of leukemia following exposure of human populations to ionizing radiation are possible. Their conclusions are as follows:

"1. Data are now adequate to indicate that, for high level, single dose exposure of man, the incidence of leukemia is approximately linear with dose. At dose levels of perhaps 100 r equivalent or greater, the incidence is approximately 1 to $2/10^6$ persons at ris/year/rad, at least from approximately the second to the fifteenth year following exposure.

"2. Below dose levels of approximately 100 r equivalent, the available data are inadequate for prediction.

"3. Data are inadequate for prediction for other than the single acute dose, *i.e.*, it is not known if a dose-rate dependency exists.

"4. It is not known if the risk continues beyond approximately the first fifteen years from exposure.

"5. Although there is evidence that large dose radiation of sizeable portions of the marrow may be leukemogenic, there are no adequate grounds for assuming that the highly localized radiation from internal emitters such as Sr^{90} and radium are or are not leukemogenic.

"6. It is not possible to determine whether or not a threshold dose for the induction of leukemia does or does not exist."

A total of 226 adequately documented cases of leukemia attributable to radiation exposure were found in the literature and are tabulated.

Carcinoma of the Larynx After Irradiation for Papilloma. T. C. Galloway, G. R. Soper, and J. Elsen. Arch. Otolaryng. **72:** 289–294, September 1960. (636 Church St., Evanston, Ill.)

The authors report a case in which there was a strong presumption that carcinoma of the larynx was due to irradiation twenty-nine years previously. In 1928–1929 papillomata were removed from the larynx of an eight-year-old boy under direct and suspension laryngoscopy on at least 19 occasions. At first, simple cup removal was done, later the bases were desiccated, and finally deeper coagulation was attempted, with care not to injure cartilage. On June 7, 1929, following removal of papillomata and desiccation, a 50-mg. radium capsule held in a forceps was moved within the limits of the larynx for half an hour. Three months later the irradiation was repeated, the dosage each time being calculated to be equivalent to 720 r in air. In September 1957 a flat, grayish, slightly irregular mass was noted just above the right side of the anterior commissure. The biopsy report was "tumor which consists of nests of well differentiated squamous cells with frequent mitoses and central cornifications." In April 1959 a wide-angle Orton type of operation was performed, with removal of the hyoid and most of the soft tissues anteriorly, including part of each thyroid lobe. Only 1 intralaryngeal area about 1 cm. wide showed evidence of

malignancy. No involved nodes were found. Convalescence was uneventful.

The following conclusions seem justifiable: (1) Previous irradiation is an important cause of carcinoma of the larynx. (2) In spite of improved safeguards, irradiation should not be used for benign conditions in which other treatment is adequate.

One photomicrograph.

Progress of Medical Science. Gynecology and Obstetrics. Radiation Safety in Obstetric-Gynecologic Practice. Franklin L. Payne. Am. J. M. Sc. **240:** 782–791, December 1960. (University of Pennsylvania, School of Medicine, Philadelphia, Penna.)

The harmful responses to irradiation fall into two major categories: (1) the somatic effects which depend on exposure of the body tissues and are primarily of concern to the patient, and (2) the genetic effects which follow exposure of gonadal tissue and are of long-range concern to the human race. From the clinical point of view the genetic effects of radiation exposure are best discussed in relation to the time of exposure, either preconceptional or post-conceptional. With the former, the hazards are those of heredity. Various reports on this subject are reviewed, most of which have appeared in RADIOLOGY in original papers or in abstract form. With post-conception irradiation, the hazards are both somatic and genetic.

Diagnostic roentgenology arouses the chief concern over both adult gonadal irradiation and that to the growing fetus. The following figures are given for the radiation dose for various radiographic procedures:

1. Chest: 0.9 to 3.0 mr
2. Lumbosacral spine (anteroposterior and lateral): 365 to 1,500 mr
3. Sacroiliac joints: 720 to 800 mr
4. Barium enema: 616 to 740 mr
5. Intravenous urogram (renal): 175 to 600 mr
6. Intravenous urogram—kidneys and bladder: 1,200 to 1,300 mr
7. Hysterosalpingogram: 1,910 to 3,500 mr
8. Pelvis, bony: Anteroposterior 80 to 225 mr, plus lateral 1,300 mr
9. Obstetrical abdominal: 160 to 260 mr
10. Pelvimetry (anteroposterior and lateral): 530 to 2,160 mr

It is stressed that these data are based on the work of highly skilled radiologists and may not be representative of the "run of the mill" technics. The wide range of values is explained by the variations in the size of the subjects, equipment, and technic. Norwood *et al.* (Am. J. Roentgenol. **82:** 1081, 1959) found that 78 per cent of the entire gonadal dose came from only 6 per cent of the diagnostic examinations, *i.e.*, those involving the lower back, the abdomen, the pelvis and thighs. Thirty-seven per cent of the dose came from fluoroscopic examination of the lower gastrointestinal tract.

In summary, the author quotes Quimby (Bull. Sloane Hosp. for Women **6:** 1, 1960) to the effect that the critical period for irradiation of the fetus is in the first few weeks, before the existence of pregnancy may have been established. During the last five months of pregnancy, the fetus should not be damaged by doses in the order of those from pelvimetry. Such examinations should be conducted only when there is real indication for them, and as late in pregnancy as possible. It must be remembered that x-rays, properly used, are a powerful instrument for good. Particularly when a pregnant mother and a fetus are concerned, the good to be hoped for must be weighed against the possible hazardous effects. It is better that the obstetrician should know the actual situation than that the mother and baby run grave risks in order to avoid the less tangible ones.

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Radiation Protection for Users of the Nasopharyngeal Radium Applicator. Arthur T. Ward, Jr. Arch. Otolaryng. **72:** 385–387, September 1960. (11 Chase St., Baltimore 2, Md.)

The author describes three protective devices used in conjunction with one another in giving radium therapy to the nasopharynx.

(1) An improved Crowe-Burnam nasopharyngeal 50-mg. radium applicator has a total length of 15 in. as compared to 7 in. for the standard model. A stainless-steel wire, which is welded on either side of the applicator for a distance of 6 in., goes through the radium-containing head to prevent its loss, should it fracture, in the nasopharynx or esophagus.

(2) An enlarged and improved storage container for holding the applicator is made of brass, is 10 in. deep with a 3/4-in. diameter, and can be filled with 70 per cent alcohol. It sits in the center of a lead chamber 7 in. in diameter and 6 in. deep, which can be angled toward a window so that any rays can be directed outdoors.

(3) A lead-lined treatment table is leaded on 3 sides with 1-in. lead plate to protect the operator, and its floor has a 1/2-in. lead plate along its entire length.

Ionization-chamber studies show that these devices give excellent protection. With most of the operator's body protected except for hands and arms, with exposures of thirty seconds for each treatment, he could safely give 120 treatments a week.

Three photographs; 1 table.

Thorotrast-Induced Cancer in Man. Renato Baserga, Hidejiro Yokoo, and George C. Henegar. Cancer **13:** 1021–1031, September-October 1960. (VA Research Hospital, Chicago, Ill.)

Another case of Thorotrast-induced cancer is reported, bringing to 37 the number of proved cases recorded in the literature (excluding all cases of leukemia). The data on the previous cases are presented in tabular form.

The authors' patient was a 37-year-old man who died with a bile-duct carcinoma of the liver fourteen years after the injection of Thorotrast into a liver abscess. On roentgen examination there were three noteworthy findings: (1) two opacities, one located in the mid-line in the region of the anterior edge of the liver and the other at the right lateral edge of the liver; (2) flake-like deposits throughout the liver and in the region of the spleen; (3) smaller homogeneous densities along the lesser curvature of the stomach and extending toward the porta hepatis. At autopsy, Thorotrast deposits were found in the liver, spleen, bone marrow, lymph nodes, and, to a lesser degree, in the testes, suprarenal glands, kidneys, and lungs.

Clinical diagnosis of the presence of Thorotrast, in the absence of a clear history of Thorotrast injection, rests on three findings—the demonstration of radiopaque deposits in the liver and spleen, physical detection of radioactivity in the body of the patient, and biopsy confirmed by autoradiography.

The radiation dosage calculation is discussed.

The authors emphasize three points: (1) the need for a thorough follow-up of Thorotrast cases; (2) the fact that the liver and not the bone should be considered the critical organ of deposition of thorium and its daughter elements; (3) the relatively small amount of thorium required to produce a malignant tumor.

Ten figures, including 1 roentgenogram; 3 tables.

H. N. STURTEVANT, M. D.
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Carcinoma of the Maxillary Sinus Following Thorotrast Instillation. Report of 3 Cases. Morton Kligerman, Raffaele Lattes, and Robin Rankow. Cancer **13**: 967–973, September-October 1960. (Yale University School of Medicine, New Haven, Conn.)

The authors report 3 cases of carcinoma of the maxillary sinus occurring in patients upon whom intrasinusal instillation of thorium dioxide (Thorotrast) was performed ten, eighteen, and twenty-one years earlier for diagnostic purposes. Histologically, one tumor was an adenocarcinoma, one a squamous-cell carcinoma, and the third a mucoepidermoid carcinoma. A fourth case is presented in an addendum. Roentgenograms in all 4 cases showed remnants of radiopaque material in the maxillary sinuses.

The authors consider the cause-and-effect relation between Thorotrast and the subsequent cancers "highly probable" and believe that these cases add to the existing evidence that Thorotrast is carcinogenic and should not be employed as a diagnostic medium.

Three roentgenograms; 8 photomicrographs.

H. N. STURTEVANT, M.D.
Springfield, Mo.

Amount of Irradiation Received by Swiss Population by Roentgen Diagnostic Procedures. A. Zuppinger, W. Minder, R. Sarasin, and M. Schaer. Radiol. clin. **30**: 1-27, January 1961. (In German) (Röntgeninstitut der Universität Bern, Switzerland)

The authors report an extensive radiation survey made in Switzerland with the help of doctors and hospitals. In 1958, 5,018,500 roentgen examinations were made in a resident population of 5,160,000. Chest studies were the most frequently performed. Every third examination was done by screening only. The most significant amounts of irradiation from the genetic standpoint resulted from pyelography, followed by examinations of pregnant women and investigations of the pelvis. The average genetically significant amount of irradiation amounts to 22.3 mr/year.

One figure; 12 tables.

CHARLES M. NICE, JR., M.D., PH.D.
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Physiological Vigor as a Factor in Radiation Reduction of Lifetime Fertility of Mice. Loren H. Haverland and John W. Gowen. Radiation Res. **13**: 356–368, August 1960. (Iowa State University, Ames, Iowa)

Littermate pairs of mice of five inbred strains and all their possible F_1 hybrids were given equal doses of 100-kvp x-rays at 2.5 ma at six weeks of age. After x-ray exposure, the pairs were mated for life. The x-ray doses were 0, 20, 200, 400, and 800 r. Each of the 125 combinations of doses and inbred and F_1 hybrid strains was represented by at least two matings. The following radiation and genetic effects on lifetime fertility were shown or suggested by the data obtained:

1. The lifetime fertility of matings was drastically reduced when the pairs were exposed to acute x-ray doses of 200 r or more. Pairs exposed to 800 r produced one litter at most. But one-fourth of the matings exposed to 200 r produced two litters.

2. The effects of radiation on lifetime fertility were quite severe in comparison with the effects on some other vital functions investigated. The relation of radiation dose and lifetime progeny closely follows an exponential pattern expressed in the equation $y = ae^{-bd}$, where y is the expected lifetime number of young, a and b are constants, e is the base of natural logarithms, and d is the dose in roentgens.

$$\text{Inbred progeny} = 33.5e^{-0.0097\ \text{dose}}$$
$$\text{Hybrid progeny} = 74.7e^{-0.0061\ \text{dose}}$$

3. The reduction of fertility at high dose levels was predominantly due to the effects of radiation on the females. Most irradiated males proved fertile when mated with unirradiated females.

4. In the unexposed group, the average lifetime progeny for all hybrid pairs was three times as great as that for all inbred pairs. This difference persisted and was statistically significant with all x-ray exposures. When sterile matings were excluded, the difference remained significant with all x-ray exposures. The difference was not statistically significant with the 200- and 800-r exposures when pairs that had less than two litters were excluded but was highly significant with the 0-, 20-, and 400-r exposures.

The evidence suggests that the inbred mice were more severely affected by x-ray exposure than were the hybrid mice. None of the matings, inbred or hybrid, were sterile with the 0- and 20-r exposures. The proportion of sterile matings was greater for the inbreds than for the hybrids with 200- and 400-r exposures. Several interpretations of this genetic difference are discussed. It is pointed out that the low fertility of the inbreds as contrasted to the hybrids resulted in more pairs being completely sterile when exposed to the higher dosages of irradiation. Hybrid vigor, by increasing F_1 fertility threefold, increased the viabilities of the eggs to x-irradiation by one-third and reduced the apparent sterility of the mated pairs of mice.

One figure; 2 tables. AUTHORS' SUMMARY

Studies on Radiation-Induced Mammary Gland Neoplasia in the Rat. IV. The Response of Females to a Single Dose of Sublethal Total-Body Gamma Radiation as Studied until the First Appearance of Breast Neoplasia or Death of the Animals. C. J. Shellabarger, V. P. Bond, and E. P. Cronkite. Radiation Res. **13**: 242–249, August 1960. (V. P. B., Medical Research Center, Brookhaven National Laboratory, Upton, N. Y.)

It has been established by the authors that a single sublethal total- or partial-body x- or gamma-ray exposure of the male or female young Sprague-Dawley rat results in the relatively early appearance of neoplasia of the breast. (Radiation Res. **12**: 81 and 94, 1960. Abst. in Radiology **76**: 701, 1961). Further, the neoplastic response of the breast of the female seems to be related directly to the dose, within the range studied (Radiation Res. **12**: 276, 1960. Abst. in Radiology **76**: 862, 1961), and to depend on a direct radiation effect on the breast tissue (Radiation Res. **13**: 318, 1960. See abstract which follows) and on gonadal hormones as well. All of the studies mentioned were performed

within ten to sixteen months postexposure, at which time the incidence of breast pathology of the nonexposed rats and the nonbreast pathology of exposed and nonexposed rats was relatively low. In the present paper the authors report data on the incidence of breast and nonbreast tissue pathology after a single dose of 200 or 400 r of total-body Co^{60} gamma-radiation delivered on the fortieth day of age to female Sprague-Dawley rats as studied until all animals were dead or had exhibited at least one neoplasm of the breast. The findings were as follows:

1. Final cumulative incidence of rats with one or more histologically verified neoplasms of the breast was: control, 12 of 30 = 40 per cent; 200 r, 18 of 28 = 64 per cent; 400 r, 27 of 30 = 90 per cent.
2. Total number of neoplasms of the breast: control, 15; 200 r, 36; 400 r, 58.
3. Final cumulative incidence of rats with neoplasms of nonbreast tissue: control, 23 per cent; 200 r, 43 per cent; 400 r, 37 per cent.
4. Cumulative incidence of rats with breast and nonbreast neoplasms at eleven months postexposure: control, 3 per cent and 0 per cent; 200 r, 36 per cent and 4 per cent; 400 r, 60 per cent and 7 per cent.
5. The histological types of breast neoplasms, in decreasing order of occurrence, were: adenofibroma, fibroadenoma, adenocarcinoma, and fibrosarcoma. The proportion of these histologic types was not different in the three groups of animals, but adenofibromas and adenocarcinomas appeared sooner in the exposed than in the nonexposed animals.

It was suggested that a linear dose-neoplastic response relationship, observed previously when the animals were studied for eleven months, might hold over the entire life span, since the data here reported indicate that 400 r produced a neoplastic response of the breast approximately twice that observed after 200 r. It was not possible, however, to choose between two possibilities: (1) Irradiation induces more neoplasms than occur in nonexposed rats, or (2) Irradiation hastens the onset of neoplasia of the breast.

Two figures; 1 table.

Studies on Radiation-Induced Mammary Gland Neoplasia in the Rat. V. Induction by Localized Irradiation. V. P. Bond, C. J. Shellabarger, E. P. Cronkite, and T. M. Fliedner. Radiation Res. **13**: 318–328, August 1960. (Medical Research Center, Brookhaven National Laboratory, Upton, N. Y.)

Previous studies from the Brookhaven National Laboratory (see preceding abstract) showed that a single large whole-body x-ray exposure of Sprague-Dawley rats was followed in months by a large increase in the incidence of mammary gland neoplasia. In addition, the dose-effect relationship seemed to be linear within limits, and intact ovarian function was found to be necessary for maximum incidence of neoplasia.

In the experiments described here, designed to determine if the breast tissue must be directly Irradiated for maximal neoplasia induction, groups of approximately 30 female Sprague-Dawley rats were irradiated on the fifty-fifth day of age as follows: 400 r total-body irradiation; 400 r entire left half of body; 400 r to chest; 400 r to lower half of body; 400 r with one hind limb shielded; and 400 r through a grid. With half-body exposure and with exposure through the grid, approximately one-half of the total number of neoplasms seen after total-body irradiation was observed. Shielding of the leg had no effect on the incidence of neoplasia. With half-body irradiation, more than 90 per cent of all breast neoplasms occurred in tissues exposed directly to the beam. The results indicate clearly that direct radiation injury to the breast is necessary for an increased incidence of radiation-induced neoplasia under the conditions employed.

It appears from these and previous studies that radiation-induced "primary" damage in the target organ is necessary for an increased incidence of the neoplasia observed, but that the primary damage may lie dormant and not manifest itself maximally as neoplasia unless an additional secondary mechanism (presumably cyclic ovarian activity in the data presented) is operative. The implications of the results with respect to a possible somatic mutation mechanism of radiation neoplasia induction are discussed.

Two figures; 2 tables.

Autoradiographic Study with Tritiated Thymidine of Mouse Testis after 320 r and after 1000 r of Acute Localized X-Irradiation. Bernard R. Nebel, Carol J. Murphy, and Harris J. Linder. Radiation Res. **13**: 126–136, July 1960. (Argonne National Laboratory, Argonne, Ill.)

Two groups of C57 black male mice approximately one hundred days old were given 320- and 1,000-r doses of acute localized x-irradiation, respectively, to the testes. The 320-r animals were injected with tritiated thymidine ten to fifteen minutes before exposure; the 1,000-r series, twenty-four hours previously. One-half of the 320-r animals were sacrificed at two to forty-eight hours and the remainder at three to twenty-eight days; fixation of the testes was carried out and sections were prepared for autoradiography. Animals in the second group were sacrificed at one to twenty-eight days after irradiation.

The distribution of stages of tubules showing labeled cells was compared in 320-r and control material and found to be synchronous. After 320 r the respective range of stages at each sacrifice date was narrower than in the control, owing to selective killing of type B spermatogonia. Thus, a narrower stream of labeled cells is fed into early meiosis. With 1,000 r, synchrony also exists as long as cells are present to maintain it.

Cell death is not limited to spermatogonia. After 320 r, there is also some loss of spermatocytes and a severe loss of spermatids over and beyond the loss resulting from diminished recruitment.

The thymidine label made it possible to trace labeled restitution cells from their original position in the tubule to the basement membrane, but the present study allows no statement concerning their life span and ultimate fate.

Four graphs; 1 table.

Postirradiation Protection of X-Irradiated Mice with Olive Oil. James K. Ashikawa and Orland K. Anderson. Radiation Res. **13**: 99–107, July 1960. (Donner Laboratory of Biophysics and Medical Physics, Berkeley, Calif.)

The accumulation of fats and lipids in organisms after whole-body irradiation has been observed by a number of investigators. This may be due to an abortive attempt by the organism to recover from the injury. If this is the case, the administration of fats to irradiated animals may have some beneficial effect. The authors

describe experiments designed to determine the effect of olive oil in irradiated mice. The protective effect of lycopene was also evaluated.

Ellinger *et al.* (Radiology **64:** 210, 1955) demonstrated the reproduciblity of lethality in whole-body x-irradiation in the midlethal range through strict adherence to certain physical and biological experimental precautions. A comparative experiment is presented to illustrate the importance of such rigorous biological control.

Four hundred and sixty-four male Swiss white mice, six to eight weeks old and weighing 26 ± 4 gm., were given total-body irradiation in a single exposure at a dose rate of about 9 r/min. A single intraperitoneal injection of 1 ml. of pharmaceutical-grade olive oil was administered within an hour before or within a half-hour after irradiation. In all three lethal doses tested, the olive oil had some protective effect, with increase in survival most pronounced in the midlethal group (LD 50/30 to LD 60/30), where almost 90 per cent of the postirradiation oil-treated animals survived. The treated animals lost much less weight and regained any loss much more rapidly than the controls.

In the authors' hands the intraperitoneal administration of lycopene had a questionable effect on irradiated mice.

Six figures; 2 tables.

Modification of the Radiation Effect on Tumors by Cortisone in Intact and Adrenalectomized Animals. Henry P. Plenk and Roger B. Fuson. Cancer **13:** 1188-1194, November-December 1960. (St. Mark's Hospital, Salt Lake City, Utah)

In a study reported in 1959 (Radiology **72:** 75, 1959), the authors found that the administration of ACTH and cortisone reduced the incidence of metastases of neuroblastoma C1300 and increased the seventy-day survival of irradiated mice inoculated with this tumor and with two mammary carcinomas. The purpose of the investigation described here was to quantitate the synergistic effect of x-rays and cortisone to the administered dose of the drug. Adrenalectomy was employed to pinpoint the action of cortisone by eliminating other possible adrenal influences.

Following the anterior chamber transplantation of two mammary carcinomas and one neuroblastoma into susceptible strains of intact mice, x-irradiation (3,000 r) to the orbit on the fourth post-transplant day resulted in 45 per cent survivals at the end of seventy days. The administration of cortisone plus x-rays increased the percentage of survivals to 71 per cent.

Of the adrenalectomized animals receiving therapeutic doses of cortisone plus x-rays, 30 per cent survived seventy days compared to 43 per cent of the animals receiving only a maintenance dose of cortisone plus x-rays. The cortisone effect was apparent when the hormone was given at the time of irradiation. Prolonged administration did not increase the percentage of survivors.

A dose of 0.05 mg. of cortisone (2.5 times the maintenance dose) was at least as effective as larger doses as expressed in the number of mice surviving seventy days.

The synergistic cancericidal effect of cortisone and irradiation is assumed to be due to a modification of the radiation sensitivity of the tumor and not to a direct effect of cortisone on tumor growth *per se*.

No evidence was found to suggest that the simultaneous administration of cortisone and x-ray therapy has any harmful effects. If animal experience could be applied to man, the combined effect might prove to be beneficial in increasing the radiation response of some tumors.

Five graphs; 2 tables.

Cysteine Protection Against X-Rays and the Factor of Oxygen Tension. Henry I. Kohn and Shirley E. Gunter. Radiation Res. **13:** 250–255, August 1960. (University of California School of Medicine, San Francisco 22, Calif.)

Protection experiments were carried out with washed suspensions of *Escherichia coli* B/r that were suspended in buffer, exposed to 0.1*M* L-cysteine at 22 to 24° C., and then irradiated with 250-kv x-rays of 0° C. Trials were made with suspensions in equilibrium with 0, 5, 20, and 100 per cent oxygen at the time of irradiation, at *p*H 5 and at *p*H 7.8.

L-Cysteine afforded significant protection under all conditions. The mode of action of cysteine therefore includes one reaction that can occur independently of oxygen. The independence is both biologic and radiologic, *i.e.*, oxygen is not needed for cysteine to reach the sensitive locus prior to irradiation, nor is it needed at the time of irradiation. Further studies are wanted to establish the relation, if any, of this protective reaction to the sensitizing reaction which involves oxygen.

It was also shown in tests at *p*H 7.4 to 7.8 that the ethyl ester of L-cysteine and D-cysteine protect under anoxic conditions; D-cysteine, however, was significantly less potent than L-cysteine at *p*H 5.

One table. AUTHORS' SUMMARY

Protection against Irradiation Afforded by Sodium Fluoroacetate. Z. M. Bacq, S. Liébecq-Hutter, and C. Liébecq. Radiation Res. **13:** 286–297, August 1960. (Laboratoire de pathologie générale, Université de Liège, Belgium)

The protection against irradiation afforded by sodium fluoroacetate (4 to 5 mg./kg.) was studied in nearly 200 C57 black male and female mice. The animals were divided into four groups—one group was treated by x-rays only, one by sodium fluoroacetate only, one by fluoroacetate five hours before irradiation, and one by fluoroacetate immediately before or after irradiation. Death caused by fluoroacetate poisoning always occurs before the fourth day, most generally within the first two days.

It was found that the injection of sodium fluoroacetate immediately before or after irradiation had no effect on mortality. If injected five hours before irradiation, however, it reduced the mortality produced by 650 to 675 r of whole-body irradiation. After seven days, 42 per cent of the mice receiving irradiation only had died, whereas mice preinjected with sodium fluoroacetate were all alive. After fourteen days, the mortality figures for the two groups were 90 and 20 per cent; after twenty-one days, 94 and 40 per cent. No deaths occurred after that time in any of the experimental series.

The high levels of citric acid in the tissues of the fluoroacetate-poisoned animals returned to normal within twenty-four hours if 675 r of x-rays were given five hours after 5 mg./kg. of sodium fluoroacetate, whereas forty-eight hours were required in the case of nonirradiated control mice. Thus, irradiation interfered with the metabolism of citric acid in the tissues of the mouse, as has been reported in the rat. The liver

of the mouse, however, did not behave like the liver of the rat. In contrast to rats, male mice injected with sodium fluoroacetate accumulated citrate in their livers, whereas females did not; whole-body irradiation reduced the level of accumulated citrate in the liver as it did in other tissues of the mouse.

The injection of sodium fluoroacetate produced a prolonged hypothermia.

It is suggested that the fluoroacetate-induced accumulation of citrate protects the animals by complexing magnesium ions necessary for deoxyribonuclease activity.

Three figures.

Effect of Graded Acute Exposures of Gamma Rays or Fission Neutrons on Survival in Subsequent Protracted Gamma-Ray Exposures. J. F. Spalding, V. G. Strang, and F. C. V. Worman. Radiation Res. **13:** 415–423, September 1960. (Los Alamos Scientific Laboratory, Los Alamos, N. Mex.)

Five hundred and twenty-eight female mice were randomly divided into twelve groups and given fractionated doses of γ-rays ranging from 240 to 1,200 rads and fission neutrons ranging from 92 to 451 rads. After a repair period of ninety days, they were placed in a continuous field of γ-rays (50 rads per twenty-four hours), where they remained until death. The mean accumulated dose for each group was determined and correlated with the insult dose. The results of this study showed that: (1) Radiation-induced damage in the mouse has one component that is permanent and irreversible. (2) At least a fraction of this irreversible damage is proportional to the magnitude of the insult dose and is measurable in terms of a reduction in survival time in a continuous γ-radiation field. (3) The fraction of permanent injury produced by fission neutrons is approximately five times as great as that produced by γ-rays.

A comparison of the results of this study with others of a similar nature was made.

One figure; 3 tables. AUTHORS' SUMMARY

Survival of Guinea Pigs after Lethal Irradiation and Homologous Bone Marrow Injections. Stanley A. Rosenthal, Leonard C. Harber, Rudolf L. Baer, and Milton Friedman. Radiation Res. **13:** 496–501, September 1960. (New York University Post-Graduate Medical School, New York, N. Y.)

In a few experiments (see, for example, Lorenz *et al.*, Radiology **58:** 863, 1952), inbred guinea-pigs receiving normally lethal doses of radiation have manifested prolonged survival after isologous bone-marrow transfusions. The authors describe an attempt to determine whether heterozygous lethally-irradiated guinea-pigs could be similarly protected by homologous marrow. The ability of these irradiated animals to accept homologous skin grafts was also investigated.

The lethal effect of whole-body x-irradiation (450, 600, 675, 750, 825, or 900 r) was studied in 299 heterozygous English short-haired male albino guinea-pigs. The LD 100/15 days was found to be 675 r.

By using homologous bone-marrow transfusions after lethal whole-body irradiation in 168 guinea-pigs, in doses ranging from 675 to 900 r, a thirty-day survival of 12 to 21 per cent (median 18.5 per cent) was achieved.

This heterozygous group of guinea-pigs in general was unable to survive skin homografts from the donor of the bone marrow immediately after whole-body x-irradiation. In the 2 animals surviving these three procedures for several weeks, however, the skin homografts also survived.

One figure; 4 tables.

The Relative Biological Efficiency of 20-Mev Electrons and 180-Kvp X-Rays in Escherichia coli Inactivation. Irving Leskowitz, J. G. Van Dyke, J. S. Laughlin, and J. J. Nickson. Radiation Res. **13:** 445–451, September 1960. (Sloan-Kettering Institute, New York)

The relative biological efficiency of 20-Mev electrons as compared with 180-kvp x-rays was determined from dose-survival curves for *E. coli* B/r, irradiated in the resting stage. Absorbed doses produced by the 180-kvp x-rays were measured with the Fricke ferrous sulfate dosimeter on the basis of Victoreen chamber measurements with correction and conversion factors applied as described. The absorbed dose of electrons was determined with the Fricke ferrous sulfate dosimeter and a G value of 15.5 molecules of ferric ion produced per 100 ev. The relative biological efficiency was found to be 0.82 $\pm$ 0.1 with *E. coli* B/r.

Three figures; 1 table. AUTHORS' SUMMARY